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HIV Treatment Policy and Contact Angle of Antiritroviral Drugs

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ABSTRACT

The advent of Highly Active Antiretroviral Therapy (HAART), marked at the 11th International Conference on AIDS in 1996, revolutionized HIV treatment by introducing potent combination drug regimens that drastically reduced AIDS-related morbidity and mortality. HAART targets multiple stages of the HIV life cycle, including viral entry, reverse transcription, integration, and maturation, utilizing diverse drug classes such as entry inhibitors, reverse transcriptase inhibitors (nucleoside and non-nucleoside), protease inhibitors, and integrase inhibitors. HIV's rapid replication and high mutation rate foster the emergence of drug-resistant strains, underscoring the necessity of combination therapy to suppress viral replication and limit resistance development. Treatment guidelines have evolved to recommend earlier initiation of therapy with lifelong adherence to maximize clinical outcomes. Despite advances in drug formulations improving patient adherence, challenges remain, including adverse drug effects, resistance, treatment cost, and accessibility, particularly in resource-limited settings. Post exposure prophylaxis and treatment as prevention strategies further contribute to reducing HIV transmission. Understanding HIV's viral dynamics and the principles underlying antiretroviral drug action remain critical to optimizing treatment and curbing the global HIV epidemic. The study concluded that short life-cycle and high error rate are the cause of virus which mutate to a very rapidly rate that result in a high genetic variability of HIV. It was recommended that treatment regimens should be continue in order to utilize a multi-class approach targeting various stages of the HIV lifecycle: entry inhibitors, CCR5 antagonists, NRTIs, NNRTIs, protease inhibitors, integrase inhibitors, and maturation inhibitors.

Keywords: HIV, Treatment Policy and Contact Angle of Antiritroviral Drugs

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1. INTRODUCTION

1.1 History of HIV Treatment and Policy

The advent of HAART has been dated to the 11th International Conference on AIDS in Vancouver, British Columbia, July 7-16, 1996. During that Conference, David Ho, MD, of the Aaron Diamond AIDS Research Center, New York, NY, and George Shaw, MD, PhD, of the University of Alabama at Birmingham School of Medicine, presented viral dynamics data showing that the average person with HIV infection produced 10 billion virions/day, bringing into sharp focus the fact that this was a viral infection that required antiviral treatment. The conference was followed by sequential publications in The New England Journal of Medicine by Hammer and colleagues and Gulick and co-investigators illustrating the substantial benefit of indinavir-based HAART. This concept of 3-drug therapy was quickly incorporated into clinical practice and rapidly showed impressive benefit with a 60% to 80% decline in rates of AIDS, death, and hospitalization.

1.2 Categories of Antiretroviral Drugs

Antiretroviral (ARV) drugs are broadly classified by the phase of the retrovirus life-cycle that the drug inhibits. They include the following as stated below

- Entry inhibitors (or fusion inhibitors) interfere with binding, fusion and entry of HIV-1 to the host cell by blocking one of several targets. Maraviroc and enfuvirtide are the two currently available agents in this class.
- CCR5 receptor antagonists are the first antiretroviral drugs which do not target the virus directly. Instead, they bind to the CCR5 receptor on the surface of the T-Cell and block viral attachment to the cell. Most strains of HIV attach to T-Cells using the CCR5 receptor. If HIV cannot attach to the cell, it cannot gain entry to replicate.
- Nucleoside reverse transcriptase inhibitors (NRTI) and nucleotide reverse transciptase inhibitors (NtRTI) are nucleoside and nucleotide analogues which inhibit reverse transcription by being incorporated into the newly synthesized viral DNA strand as faulty nucleotides; they both act as competitive substrate inhibitors.
- Non-Nucleoside reverse transcriptase inhibitors (NNRTI) inhibit reverse transcriptase by binding to an allosteric site of the enzyme; NNRTIs act as non-competitive inhibitors of reverse transcriptase.
- Protease inhibitors (PIs) target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for the final assembly of new virions.
- Integrase inhibitors inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell. There are several integrase inhibitors currently under clinical trial, and raltegravir became the first to receive FDA approval in October 2007.
- Maturation inhibitors inhibit the last step in gag processing in which the viral capsid polyprotein is cleaved, thereby blocking the conversion of the polyprotein into the mature capsid protein. Because these viral particles have a defective core, the virions released consist mainly of non-infectious particles. Alpha interferon is a currently available agent in this class. Two additional inhibitors under investigation are bevirimat and Vivecon.

2. COMBINATION THERAPY

The life cycle of HIV can be as short as about 1.5 days from viral entry into a cell, through replication, assembly, and release of additional viruses, to infection of other cells. HIV lacks proofreading enzymes to correct errors made when it converts its RNA into DNA via reverse transcription. Its short life-cycle and high error rate cause the virus to mutate very rapidly, resulting in a high genetic variability of HIV. Most of the mutations either are inferior to the parent virus (often lacking the ability to reproduce at all) or convey no advantage, but some of them have a natural selection superiority to their parent and can enable them to slip past defenses such as the human immune system and antiretroviral drugs. The more active copies of the virus the greater the possibility that one resistant to antiretroviral drugs will be made.

When antiretroviral drugs are used improperly, these multi-drug resistant strains can become the dominant genotypes very rapidly. Improper serial use of the reverse transcriptase inhibitors zidovudine, didanosine, zalcitabine, stavudine, and lamivudine can lead to the development of multi-drug resistant mutations. The mutations can include the V751, F77L, K103N, F116Y, Q151M, and the M184V mutation. These mutations were observed before protease inhibitors had come into widespread use. The mutants retained sensitivity to the early protease inhibitor saquinavir. These mutants were also sensitive to the rarely used reverse transcriptase inhibitor foscarnet. Antiretroviral combination therapy defends against resistance by suppressing HIV replication as much as possible.

Combinations of antiretrovirals create multiple obstacles to HIV replication to keep the number of offspring low and reduce the possibility of a superior mutation. If a mutation that conveys resistance to one of the drugs being taken arises, the other drugs continue to suppress reproduction of that mutation. With rare exceptions, no individual antiretroviral drug has been demonstrated to suppress an HIV infection for long; these agents must be taken in combinations in order to have a lasting effect. As a result, the standard of care is to use combinations of antiretroviral drugs. Combinations usually comprise two nucleoside-analogue RTIs and one non-nucleoside-analogue RTI or protease inhibitor. This three drug combination is commonly known as a triple cocktail. Combinations of antiretrovirals are subject to positive and negative synergies, which limits the number of useful combinations.

In recent years, drug companies have worked together to combine these complex regimens into simpler formulas, termed fixed-dose combinations. For instance, two pills containing two or three medications each can be taken twice daily. This greatly increases the ease with which they can be taken, which in turn increases adherence, and thus their effectiveness over the long-term. Lack of adherence is a of resistance development in medication-experienced patients. Patients who maintain proper therapy can stay on one regimen without developing resistance. This greatly increases life expectancy and leaves more drugs available to the individual cause should the need arise.

2.1 Fixed-dose Combinations

Fixed dose combinations are multiple antiretroviral drugs combined into a single pill.

Table 2.1 Fixed-dose combinations

Brand Name	Drug Names (INN)	Date of FDA Approval	Company
Combivir	zidovudine + lamivudine	September 26, 1997	GlaxoSmithKline
Trizivir	abacavir zidovudine + lamivudine	November 15, 2000	GlaxoSmithKline
Kaletra	lopinavir + ritonavir	September 15, 2000	Abbott Laboratories
Epzicom (in USA) Kivexa (in Europe)	Abacavir + lamivudine	August 2, 2004	GlaxoSmithKline
Truvada	tenofovir/emtricitabine	August 2, 2004	Gilead Sciences
Atripla	efavirenz+ tenofovir/emtricitabine	July 12, 2006	Gilead Sciences and Bristol-Myers Squibb
Complera	rilpivirine + tenofovir/emtricitabine	August 10, 2011	Gilead Sciences and Tibote (Johnson & Johnson)
Stribild	elvitegravir + cobicistat + tenofovir/emtricitabine	August 27, 2012	Gilead Sciences

The preferred initial regimens in the United States, as of Augus 2012, are:

- tenofovir/emtricitabine (a combination of two NRTIs) and efavirenz (a NNRTI). Efavirenz should not be given to pregnant women.
- Tenofovir/emtricitabine and raltegravir (an integrase inhibitor)
- Tenofovir/emtricitabine, ritonavir, and darunavir (both latter are protease inhibitors)
- Tenofovir/emtricitabine, ritonavir, and atazanavir (both latter are protease inhibitors)

2.2 Treatment Guidelines

(a) Initiation Of Antiretroviral Therapy

Antiretroviral drug treatment guidelines have changed over time. Before 1987, no antiretroviral drugs were available and treatment consisted of treating complications from the immunodeficiency. After antiretroviral medications were introduced, most clinicians agreed that HIV positive patients with low CD4 counts should be treated, but no consensus formed as to whether to treat patients with high CD4 counts. In 1995, David Ho promoted a "hit hard, hit early" approach with aggressive treatment with multiple antiretrovirals early in the course of the infection. Later reviews noted that this approach of "hit hard, hit early" ran significant risks of increasing side effects and development of multidrug resistance, and this approach was largely abandoned. Treatment with these types of medicine can range from $10,000 to $15,000 a year.

The timing of when to initiate therapy has continued to be a core controversy within the medical community. The development of a stable consensus is hampered by the lack of randomized controlled studies with many guidelines and consensus statements basing their recommendations on observational studies. More recently, the trend has been in favor of earlier treatment of asymptomatic HIV patients, with more studies analyzing various treatment regimens in progress.
There is a consensus among experts that, once initiated, antiretroviral therapy should never be stopped. This is because the selection pressure of incomplete suppression of viral replication in the presence of drug therapy causes the more drug sensitive strains to be selectively inhibited. This allows the drug resistant strains to become dominant. This in turn makes it harder to treat the infected individual as well as anyone else they infect.

(b) Current Guidelines

The current guidelines use new criteria to consider starting HAART, as described below. However, there remain a range of views on this subject and the decision of whether to commence treatment ultimately rests with the patient and their doctor. The treatment guidelines specifically for the USA are set by the United States Department of Health and Human Services (DHHS). The current guidelines for adults and adolescents were stated on December 1, 2009. Standard antiretroviral therapy (ART) consists of the combination of at least three antiretroviral (ARV) drugs to maximally suppress the HIV virus and stop the progression of HIV disease.

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm3 (AI).
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (AI), HIV- associated nephropathy (AII), and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm3. The Panel was divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) (A/B-II).
- For patients with CD4 counts 500 cells/mm3, the Panel was evenly divided: 50% favor starting antiretroviral therapy at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).
- Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.
- Rating of Recommendations: A Strong; B = Moderate; C = Optional Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

(c) Baseline Resistance

In countries with a high rate of baseline resistance, resistance testing is recommended before starting treatment; or, if the initiation of treatment is urgent, then a "best guess" treatment regimen should be started, which is then modified on the basis of resistance testing. In the UK, there is 11.8% medium to high-level resistance at baseline to the combination of efavirenz + zidovudine + lamivudine, and 6.4% medium to high level resistance to stavudine + lamivudine + nevirapine.
Adverse effects of antiretroviral drugs vary by drug, by ethnicity, by individual, and by interaction with other drugs, including alcohol. Hypersensitivity to some drugs may also occur in some individuals. The following list is not complete, but includes several of the adverse effects experienced by patients taking some antiretroviral drugs.

(d) Regimens of Dispensing Drugs

Most current HAART regimens consist of three (3) drugs: 2 NRTIS + a PI/NNRTI/II. Initial regimens use "first-line" drugs with a high efficacy and low side-effect profile. Treatment guidelines for HIV-1 infected adults in the developed world (that is, those countries with access to all or most therapies and laboratory tests) have been provided by the International AIDS Society-USA (IAS-USA) since 1996. The IAS-USA is a 501(c)(3) not-for-profit organization in the USA (and is not related to the worldwide International AIDS Society or IAS). The IAS-USA guidelines for antiretroviral therapy are developed by a volunteer panel of experts. Its last update was published in July 2012 in the Journal of the American Medical Association.

In the 2008 update, the panel recommended that therapy be initiated before the CD4+ cell count declines to below 350/uL and be individualized for the particular patient's situation and comorbidities. For initial therapy, it recommends 2 NRTIs with either an NNRTI, a ritonavir-boosted PI or an integrase inhibitor. In antiretroviral therapy failure, the goal of subsequent treatment is suppression of HIV-1 RNA to below detection; the treatment should ideally have 3 new drugs to which the patient's virus is susceptible. Therapy in selected clinical situations is also described. The IAS-USA also sponsors the development of guidelines for the use of drug resistance testing in patients with HIV-1 infection.

Another set of guidelines (distinct from those of the IAS-USA) are provided by an expert panel convened by the U.S. Department of Health and Human Services. The preferred initial regimens in the United States, as of August 2012, are:

- Tenofovir/emtricitabine (a combination of two NRTIs) and efavirenz (a NNRTI). Efavirenz should not be given to pregnant women.
- Tenofovir/emtricitabine and raltegravir (an integrase inhibitor)
- Tenofovir/emtricitabine, ritonavir, and darunavir (both latter are protease inhibitors)
- Tenofovir/emtricitabine, ritonavir, and atazanavir (both latter are protease inhibitors)

(e) HIV Postexposure Prophylaxis (PEP)

In 2005, the Centers for Disease Control and In 2005, the Centers for Disease Control and Prevention in the United States recommended a 28-day HIV drug regimen for those that have been exposed to HIV (HIV Postexposure Prophylaxis [PEP]). The WHO recommendations on treatment are that the minimum that should be used is dual NRTIs for 28 days, with triple therapy (dual NRTIs plus a boosted PI) being offered where there is a risk of resistance. The effectiveness of this intervention has never been precisely ascertained, but postexposure prophylaxis is most effective when administered sooner, though not believed to be effective if given 72 hours after exposure.

(f) Treatment As Prevention

Antiretroviral treatment of a person with HIV was shown to prevent HIV transmission to their uninfected heterosexual partner in clinical trial HPTN 052. This study of 1763 heterosexual couples in 9 countries was planned to last 10 years, but it was stopped early for ethical reasons when it became clear that antiviral treatment provided significant protection. Of the 28 couples where cross-infection had occurred, all but one had taken place in the control group consistent with a 96% reduction in risk of transmission. In 2011, the journal Science gave the Breakthrough of the Year award to treatment as prevention.

(g) Concerns To Regimens

There are several concerns about antiretroviral regimens: The drugs can have serious side-effects, particularly in advanced disease, if patients miss doses, drug resistance can develop, providing anti-retroviral treatment is costly and resource-intensive, and the majority of the world's infected individuals cannot access treatment services, public health: Individuals who fail to use antiretrovirals properly can develop multi-drug resistant strains which can be passed onto others.

(h) Mega-HAART

If an HIV infection becomes resistant to standard HAART, there are limited options. One option is to take larger combinations of antiretroviral drugs, an approach known as mega-HAART or salvage therapy. Salvage therapy often causes additional side effects. If an HIV infection becomes sufficiently resistant to antiretroviral-drugs, treatment becomes more complicated and prognosis may deteriorate. Treatment options continue to improve as additional new drugs enter clinical trials. However, th e limited distribution of many such drugs denies their benefits to patients, particularly in the developing world.

Table 2.2 The Adverse Effects Experienced By Patients Taking Some Antiretroviral Drugs

Abdominal pain (Ritonavir)	Ingrown nails (IDV)	Nightmares (BFZ)
Alepecia (INF-alpha)	Insomnia (Emtricitabine)	Orat ulcers (ddC)
Anemia (AZT)	Jaundice	Pancreatitis (dd)
Asthenia	Lipodystrophy/HIV-associated	Paresthesia (IDV)
Cardiovascular disease/beart	lipodystrophy	Peripheral neuropathy (ddI,
attack[32]	Liver failure	ddC, d4T)
Diarrhea (Abacavir)	Malaise	Rash
Dizziness (Vertigo)	Mental confusion (EVZ)	Renal failure or
Fanconi syndrome	Migraines	insufficiency (IDV, TDF)
Flatulence (Tenofovir) Gynecomastia	Mitochondrial toxicity (ddI >	Somnolence (drowsiness)
Headache (3TC overdose)	d4T > AZT)	Stevens-Johnson syndrome
Hepatitis	Mood swings	Change in taste perception
Hyperbilirubinemia	Myalgia (AZT overdose)	Vomiting (AZT)
Hypercholesterolemia	Myopathy (AZT overdose)	Xeroderma (dry skin)
Hyperpigmentation (Emtricitabine)	Nausea (AZT)	Xerostomia (dry mouth)
	Neutropenia (AZT)	

3. CONTACT ANGLE

Historically, the interactions of solids with liquids have been investigated using contact angle goniometry. However, such a technique usually requires the solid under investigation to be a flat non-porous surface with contact angles obtained using non-reactive liquids. In general, contact angles between the extremes of non-wetting and perfect wetting ($0°<0<90°$) are used for the indirect measurement of solid surface energies.

In this region of non-spontaneous wetting, Young's equation (Equation 1) may be used to explain the relationship between the contact angle and the three interfacial tensions:

$$\gamma i \cos\theta = \gamma s - \gamma sl \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2.1)$$

Where, γL is the air-liquid interfacial tension (liquid surface tension), γs is the air-solid interfacial tension (solid surface tension) and γsL is the solid-liquid interfacial tension. Therefore, the contact angle is a function of the surface energies of the solid and the liquid and, importantly, the nature of the surrounding medium. Several methods for calculating the total surface energy and the respective contributions of polar and disperse components to the total surface energy of a solid have been published.

However, the generally preferred method, also used in this study, is based on the acid-base approach, since it has been shown to produce results with improved internal consistency compared with equation of state methods. The specific surface energy of a solid may be calculated from contact angle measurements using liquids which exhibit different and known polar and disperse components. The dynamics between the specific interactions produce a stable surface contact angle between the surface and the liquid which can be attributed to a composite of the dispersive (Lifschitz-van der Waals, γL^{LW}), acid-base (γL^{AB}) and individual positive and negative polar (γL^{+} , γL) components of the solid's surface energy and the surface tension of the liquid.

As previously stated, contact angle goniometry usually requires the solid under investigation to be a flat non-porous surface. Although compacts of powders have been used for contact angle measurements, the general utility of compacts for surface contact angle measurements is questionable since a certain level of surface roughness must be expected, complicating angle measurement. Furthermore, for many powder compacts, the contact angle measurements may be complicated by the action of surface-accessible pores, thereby decreasing the droplet volume by capillary action during measurement. In addition, the compaction of powder particulates may affect the material solid state, for example via pressure-induced crystallography changes or inducing material anisotropy, for example in compacted MCC, leading to orientation-specific results after compaction. In part, such observations have been confirmed via variation in the surface energy properties as a function of compaction force.

To address the potential 'pitfalls' that exist in measuring surface energy values from compacted particulates, alternative methods of measuring the surface energy of un-compacted systems must be developed. Two of the most common methods are capillary intrusion of liquid analytes into the powder sample and analyte adsorption onto a powder bed at infinite dilution using inverse gas chromatography (IGC). Each approach will be discussed in more detail below.

3.1 Contact Angle Description

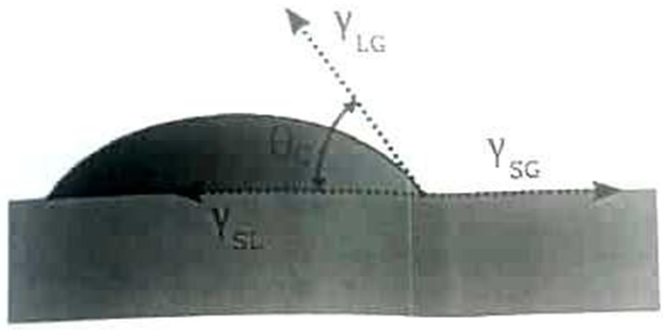

Figure 3.1 Schematic of a liquid drop showing the quantities in Young's equation.

The shape of a liquid/vapor interface is determined by the Young-Laplace equation, with the contact angle playing the role of a boundary condition. The theoretical description of contact arises from the consideration of a thermodynamic equilibrium between the three phases: the liquid phase (L), the solid phase (S), and the gas/vapor phase (G) (which could be a mixture of ambient atmosphere and an equilibrium concentration of the liquid vapor). The "gaseous" phase could also be another (immiscible) liquid phase. If the solid-vapor interfacial energy is denoted by γSGG, the solid-liquid interfacial energy by 78z, and the liquid-vapor interfacial energy by γSL (i.e. the surface tension) by γLG, then the equilibrium contact angle θcis determined from these quantities by Young's Equation:

$U = \gamma SG - \gamma SL - \gamma LG\cos\theta C$ ..... (2.2)

The contact angle can also be related to the work of adhesion via the Young-Dupré equation:

$\gamma(1 + \cos\theta c) = \Delta W_{SLV}$ .....(2.3)

Where ΔW_{SLV} is the adhesion energy per unit area of the solid and liquid surfaces when in the medium V.

(a) Contact Angle Hysteresis

On a surface that is rough or contaminated, Young's equation is still locally valid, but the equilibrium contact angle may vary from place to place on the surface. According to the Young-Dupré equation, this means that the adhesion energy varies locally - thus, the liquid has to overcome local energy barriers in order to wet the surface. One consequence of these barriers is contact angle hysteresis: the extent of wetting, and therefore the observed contact angle (averaged along the contact line), depend on whether the liquid is advancing or receding on the surface. Since liquid advances over previously dry surface but recedes from previously wet surface, contact angle hysteresis can also arise if the solid has been altered due to its previous contact with the liquid (e.g., by a chemical reaction, or absorption). Such alterations, if slow, can also produce measurably time-dependent contact angles.

The highest observed contact angle is the advancing angled θ_A, and the lowest observed contact angle is the receding angle θ_R. The contact angle hysteresis is $\theta_A - \theta_R$ OR. The Young equation assumes a perfectly flat surface. Even in such a smooth surface a drop will assume contact angle hysteresis.

The equilibrium contact angle θ_C can be calculated from θ_A and θ θ_R as was shown theoretically by Tadmor and confirmed experimentally by Chibowski as,

$$\theta c = aTCCOS(\frac{T_A COS\theta_A + T_R COS\theta_R}{T_A + T_R} \quad (2.4)$$

Where

$$T_A = \left(\frac{\sin^3\theta_A}{2-3\cos\theta_A + \cos^3\theta_A}\right)1/3, \quad T_R = \left(\frac{\sin^3\theta_A}{2-3co_R + \cos^3\theta_R}\right)1/3 \quad (2.5)$$

4. CONCLUSION

The study concluded that short life-cycle and high error rate are the cause of virus which mutate to a very rapidly rate that result in a high genetic variability of HIV. Most of the mutations either are inferior to the parent virus (often lacking the ability to reproduce at all) or convey no advantage, but some of them have a natural selection superiority to their parent and can enable them to slip past defenses such as the human immune system and antiretroviral drugs. The more active copies of the virus the greater the possibility that one resistant to antiretroviral drugs will be made.

5. RECOMMENDATIONS

The following recommendations were made

- Treatment regimens should be continue in order to utilize a multi-class approach targeting various stages of the HIV lifecycle: entry inhibitors, CCR5 antagonists, NRTIs, NNRTIs, protease inhibitors, integrase inhibitors, and maturation inhibitors.
- Government should continue the development and integration of newer drug classes, such as integrase and maturation inhibitors, are crucial to combat drug resistance and improve efficacy.
- They should continue to prescribing multi-drug regimens that will help to attack the virus at different lifecycle stages reduces the likelihood of resistant viral strains.
- Government should fixed-dose combinations simplify regimens, improving adherence and thus long-term treatment success.
- Create monitoring of resistance mutations which is the essential, particularly in regions with high baseline drug resistance.

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