Overview of antiretroviral therapy in 2019

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Introduction

Twenty years into the highly active antiretroviral therapy (HAART) era, the pace of new drug development has not slowed. Compared to its first generation, HAART of today has become more tolerable, convenient, resilient and, at the same time, less toxic. The trend of increasing rates of viral suppression has become evident.[1] Lifelong successful therapy is not only realistic but expected. In the best of circumstances, an HIV infected patient achieves a life expectancy similar to that of the general population.

HAART has exceeded all expectations. Other than treatment, it works to prevent. By lowering viral load, either on an individual or a community basis, antiretroviral serves to decrease HIV transmission. A global movement has now taken shape to widen treatment coverage of known patients at the earliest stage of infection. This optimism, however, should not detract us from using antiretrovirals with respect and great care. Never in doubt is the capability of HIV to generate resistance to multiple drugs. Antiretrovirals can also cause severe toxicity and drug-drug interactions (DDI), sometimes fatal. Therefore, it is important that only physicians experienced and knowledgeable in its use should prescribe HAART.

Rationale of antiretroviral therapy

HIV causes progressive damage to the immune system largely through loss of CD4+ T lymphocytes. Immune activation in the chronic phase allows continued HIV entry and replication. As many as 10^{10} virions are produced and cleared every day. The half-life of circulating virions is estimated to be 1-2 hours. Antiretroviral therapy interrupts crucial steps of the HIV life cycle. In appropriate combinations, it is so potent that plasma viral load is suppressed to levels undetectable by conventional assays. This has led to the concept of "HAART", which literally means using very potent antiretroviral regimen to control HIV disease. In operational terms, therapy is HAART if sustained suppression of viral load to undetectability is achieved. Upon viral suppression, immune damage is halted and in most cases reversed so that the CD4 count rises and immune capability is reconstituted. These benefits are translated clinically into decreased morbidity and mortality. With HAART, management of HIV disease has now taken resemblance to other chronic medical conditions such as diabetes.

The following principles, based on clinical studies, should be observed when prescribing antiretroviral therapy.

(a) ***Only HAART is given*** for treatment of established HIV infection. By durably reducing viral load to undetectable levels, HAART prevents the development of resistance. In general, suboptimal therapy such as single or most double therapy will allow detectable viral replication and generation of resistance. Substituting one drug in a failing regimen should therefore be avoided. While HAART normally comprises the use of 3 or more antiretrovirals, certain two-drug combinations have shown promising potency and durability in recent years that they may also arguably qualify as HAART.

(b) ***Treatment must be continuous and must remain potent throughout.*** HAART does not eradicate HIV. Even if viral replication may appear to have terminated, there is still a very low level of viraemia undetectable by conventional viral load assays, contributed by virus released from latently infected CD4 cells. [2] If therapy is interrupted, virus replication will quickly rekindle. Importantly, since replicating virus continuously enters into this cell population, all resistance that has ever happened is effectively archived in the host. Antiretroviral drugs may also fail to reach certain sanctuary sites such as the genital tract and central nervous system. This compartmentalisation may result in viral divergence, replication and resistance development.

Structured treatment interruption guided by CD4 count or fixed intervals has previously been studied, only to show that it leads to poor clinical outcome independent of the CD4 count. Surprisingly, non-AIDS complications and drug related adverse effects are more common with intermittent than with continuous treatment. It is postulated that a heightened inflammatory response associated with unsuppressed viral replication is to blame.[3]

(c) ***Adherence is crucial.*** For the first generation of HAART, compliance less than 95% was sufficient for virologic failure. Current HAART is likely more forgiving, but broadly resistant viruses can still develop. Nevertheless, fear of non-adherence should not be an excuse to withhold treatment. Instead, it should alert the physician to apply all proactive measures to foster good adherence.

Initiation of therapy

Treatment should be expeditiously initiated in a newly diagnosed patient. World Health Organization (WHO) has proposed the target of rapidly starting treatment within 7 days of a confirmed HIV diagnosis. In spite of this, the fundamental need of patient counselling and medical evaluation should NOT be overlooked, so that an optimal regimen is designed and the patient properly prepared. Rapidity of treatment should not lead to a compromised standard of care. HAART should only be given to a patient who is willing and ready.

The symptomatic patient – All HIV-associated complications are indications for HAART. In fact, certain AIDS-defining illnesses, such as progressive multifocal leukoencephalopathy and microsporidiosis, are untreatable unless by immune reconstitution secondary to effective antiretroviral therapy. Similarly, immune mediated thromobocytopaenia and lymphoma associated with HIV responds better to treatment in the presence of HAART. Understandably, the initiation of HAART in these circumstances may further complicate management in an already difficult situation. It may, for example, aggravate or unmask opportunistic infections, resulting in immune reconstitution inflammatory syndrome (IRIS). In general, HAART should be continued in the event of IRIS, but discretion should be called for if it occurs in the CNS, e.g. CNS tuberculosis and cryptococcal meningitis.

The asymptomatic patient – Until recently, the medical community has been grappling with a moving CD4 threshold to trigger treatment in an asymptomatic patient. Essentially a balance between drug toxicity and immune reconstitution, this threshold has progressively increased from 200/μL, to 350/μL, 500/μL and lately to all counts. In 2015, two landmark trials conclusively demonstrated the clinical benefit of early treatment even at very high CD4 levels.[4, 5] This knowledge has been extrapolated to those in primary infection, where expert consensus is that HAART should also be started. This recommendation is further strengthened if there are significant symptoms of seroconversion.

The public health dimension – That a public health benefit exists in preventing onward transmission is an added incentive to initiating HAART. It has been shown in a randomised controlled

trial that treatment of a patient reduces the risk of HIV transmission to his or her serodiscordant partner by 93%. Importantly, no linked infections were observed when HIV-1 infection was stably suppressed by HAART in the index participant.[6]

Choosing the appropriate antiretrovirals for the treatment-naïve patient

Although there are 'recommendations' of certain regimens to be used for the naïve patient, drug selection should not be automatic. The most appropriate regimen can only be reached after evaluating the following:

Virus characteristics

- HIV-2 is not susceptible to non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Primary drug resistance – In Hong Kong, major transmitted drug resistance relates to lamivudine (3TC), i.e. M184V, and NNRTI, such as K103N, Y181C, Y188L. Although their prevalence is estimated to be low and relatively stable,[7] the very possibility that they exist limits the use of NNRTI, but favours integrase strand transfer inhibitor (INSTI) or protease inhibitor (PI) as the initial treatment of choice.
- Level of viral load – a high viral load defined as one above 100,000/ml rules out certain regimens of lesser potency.

Patient characteristics

- The basic patient profile should include age, gender, pregnancy status, lifestyle, ethnicity, allergy history, comorbidities, HIV associated complications and current CD4 count. A relatively high CD4 count will predispose to hypersensitivity to nevirapine (NVP) (>400/μL for men and >250/μL for women). A woman's desire or potential to conceive will contraindicate the use of dolutegravir (DTG). Food restrictions, pill burden and frequency of administration of a regimen have to be evaluated for their impact on a patient's lifestyle.
- Coexisting hepatitis B and C – Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC) and 3TC are active against both HIV and hepatitis B. It is also known that the anti-HBV drug, entecavir, may lead to the development of M184V in HIV if given without HAART. A combination of TDF/TAF + FTC/3TC should be included in the treatment regimen of a patient coinfected with HIV and HBV. This combination covers both viral infections and prevents emergence of HBV resistance. In patients coinfected with hepatitis C, potential DDI with certain direct acting antivirals should also be considered.
- Cardiovascular risk profile – Non-AIDS complications have become common cause of morbidity and mortality in the HAART era. Those at high cardiovascular risk should generally avoid PI other than atazanavir (ATV). Both PI and efavrienz have unfavourable impact on lipidaemia. The role of abacavir (ABC) in causing myocardial infarct is controversial but should be avoided if alternatives are available.

Drug characteristics

- Toxicity – the expected toxicity of a regimen should be known and evaluated with a patient's unique medical history. For example, liver toxicity with NVP is particularly frequent and severe in those with chronic viral hepatitis. TDF-nephrotoxicity is more likely to occur in those with underlying kidney disease. NVP is more prone to toxicity in women and in those with high CD4 count. ATV should be avoided in patients with Gilbert' syndrome, nephrolithiasis or cholelithiasis. It is also noted that single tablet regimen and other fixed dose formulations will not allow renal dosing of its components.

- Pharmacodynamic and pharmacokinetic interaction – For one reason or another, certain combinations of antiretroviral drugs are contraindicated or disfavoured, e.g. zidovudine (ZDV) + stavudine (d4T); d4T + didanosine (ddI), TDF + ddI, 2 NNRTIs, 3TC+FTC, and etravirine (ETV)+unboosted PI. DDI at the level of cytochrome P450 are of particular concern with PI, NNRTI and boosted INSTI. Caution should be exercised when they are used with rifamycins, anticonvulsants, anti-platelet agents, steroids, anti-arrhythmic agents, oral contraceptive, etc. Antacid, H2 blockers, and proton-pump inhibitors may also impede absorption of ATV and rilpivirine (RPV).

HAART regimens for initiating therapy

In Hong Kong, five classes of more than 20 antiretroviral agents are currently in use, some of which are formulated as fixed dose combination. The five classes are (a) nucleoside reverse transcriptase inhibitors (NRTI), (b) non-nucleoside reverse transcriptase inhibitors (NNRTI), (c) protease inhibitors (PI), (d) integrase strand transfer inhibitors (INSTI), and (e) entry inhibitors. The entry inhibitors comprise a diverse group of drugs, including the CD4 antibody, ibalizumab, the fusion inhibitors, enfuvirtide and albuvirtide, and the CCR5 antagonist, maraviroc (MVC). The generic formula of HAART for the treatment-naïve is: Two NRTI + one boosted PI/one NNRTI/one INSTI/MVC. The 2 NRTI, being the common factor, is often referred to as the backbone. Differences exist among the members of each drug class. The design of a particular combination should strive for the optimal balance between drug potency, tolerability, toxicity and patient acceptance.

The INSTI-containing regimen – Current members of the INSTI group include raltegravir (RAL), dolutegravir (DTG), elvitegravir (EVG) and bictegravir (BIC). They are currently the favoured choice for initial therapy of the treatment-naïve because of rare primary resistance, good tolerability and generally lesser potential of DDI. However, all INSTI are not the same. EVG requires pharmacokinetic boosting by cobicistat (COBI) with all its potential for DDI. Other than RAL, all INSTIs are available as fixed dose combinations with two NRTIs as single tablet regimens. DTG is also coformulated with rilpivirine, an NNRTI. Genetic barrier is low for RAL and EVG, and cross resistance between them is common. But the barrier is much higher with DTG and BIC. A long acting injectable INSTI, cabotegravir, is being developed.

Boosted PI-containing regimen - There is extensive track record of PI-based HAART. PIs in use today include darunavir (DRV), ATV, and lopinavir (LPV). Darunavir is generally favoured as it is either better tolerated or more convenient than the others, resulting in superior clinical effectiveness.

PI should be given with the pharmacokinetic booster of ritonavir (RTV) or COBI. Other than inhibiting metabolism of PIs by the cytochrome P450 enzymes, RTV enhances the cellular penetration of PIs which are substrates of the P-glycoprotein system. Pharmacokinetic boosting has been credited as the reason behind the high genetic barrier characteristic of PI-based regimens. Multiple resistance-associated mutations are generally required for full PI resistance and cross resistance. By increasing the dosage of PI and/or its booster, it may also be possible to overcome partial resistance. For added convenience, LPV is coformulated with RTV as Kaletra®, and DRV with COBI as Prezcobix®. Recently, the single tablet regimen of Symtuza® has been made available which consists of TAF, FTC, DRV and COBI.

NNRTI-containing regimen – In 1996, the triple regimen of ZDV/ddI/NVP was shown to be superior to a double-nucleoside regimen, resulting in prolonged viral suppression. Subsequently, another prospective trial showed that efavirenz (EFV)-based HAART surpassed an indinavir (a PI) -based regimen. Thus was established the potency and durability of a regimen comprising 2 NRTIs + 1 NNRTI. Newer additions to this class include rilpivirine (RPV), etravirine (ETR) and doravirine (DOR).

However, it must be cautioned that NNRTI has a low genetic barrier, with one mutation being sufficient to generate high level resistance. Viral fitness is minimally impaired by these mutations. Worldwide, including Hong Kong, primary resistance to NNRTI exceeds that to PI or NRTI. Cross resistance between NVP and EFV is also common. However, the newer RPV, ETR and DOR are not affected by certain NNRTI mutations *in vitro* and may be useful for salvage situations.

There is also some concern that Asians could be more prone to the CNS effects of EFV because of the common occurrence of CYP2B6 polymorphism.[8] Because of relatively low potency, neither NVP nor RPV is recommended when the pre-treatment viral load is higher than 100,000/ml. In general, NNRTI-based treatment is not favoured for rapid treatment initiation when resistance results are usually not available yet. The single tablet regimen of DOR, TDF and 3TC (Delstrigo®) has recently been approved. A long acting injectable formulation of RPV is also being developed.

The MVC-containing regimen – MVC is unique among antiretrovirals in targeting the CCR5 molecule on host cell membrane. In doing so, it inhibits the entry of HIV viruses that use CCR5 as the coreceptor. It is effective in clinical trials, but it requires the prior use of the expensive enhanced sensitivity phenotypic test (Trofile ES) to exclude CXCR-4 using viruses. Genotypic assay may be considered but it is not a proven alternative. The potency and durability of an MVC-based regimen as first line treatment is based on only a small number of trials. Furthermore, its mechanism and monitoring of resistance are not well defined. MVC has never been a popular choice among doctors and patients.

The NRTI backbone – The old practice of using almost any two NRTI as the backbone is now replaced with specific recommendations: 3TC or FTC should be combined with TDF, TAF or ABC. The respective co-formulated pills of Truvada®, Descovy®, and Kivexa® are now the most commonly used NRTI backbone if single tablet regimens are not given. However, there is evidence that ABC is outperformed by TDF in patients with high baseline viral load, except when ABC is used in combination with 3TC and DTG (as in the combination pill of Triumeq®). All NRTIs can potentially cause mitochondrial toxicity, but it is especially likely with ZDV, d4T and ddI. The latter two drugs are no longer in use in Hong Kong. For ABC, potentially fatal hypersensitivity can occur, usually in those with HLA- B*5701 which is relatively common with Caucasians but very rare with ethnic Chinese. Its screening is considered unnecessary for Chinese. TDF may also be complicated by nephropathy, including Fanconi syndrome, and decreased bone mineral density. These adverse effects are lessened with TAF which carries a lower dosage of tenofovir. TAF, however, results in higher levels of LDL and HDL cholesterol, and triglycerides than TDF, the clinical significance of which is unclear.

Unconventional drug regimens

Two-drug regimen – the benefit of using two NRTI originates from the greatly reduced viral fitness should resistance to one emerge. Many two-drug combinations using one or no NRTI have been studied and most have failed as maintenance therapy. They include ATVr+RAL, MVC+PI, and MVC+RAL, all of which are associated with high rates of virologic failure. Some other combinations, however, have shown varying degrees of success. Currently, these two-drug regimens are limited to circumstances where it is desirable to limit or spare the use of NRTI. Boosted PI+3TC, RAL+ DRVr/DRVc, DTG+RPV (coformulated as Juluca®)[9] and DTG+3TC have shown effectiveness in switch from patients with sustained viral suppression and without known or suspected resistance. Recently, the combination of DTG+3TC has shown promise as initial treatment in clinical trials.[10]

Triple NRTI - Multiple options of effective and easily tolerable HAART being available, triple NRTI regimen is no longer justified even for those with low viral load. Previously, the combinations of AZT/3TC/ABC (Trizivir®) and TDF/ZDV/3TC have been used. Of note, certain triple NRTI combinations are contraindicated. TDF/3TC/ABC, TDF/ddI/3TC, and d4T/ddI/ABC all have inferior

potency. Their failures are often associated with the development of K65R which causes broad resistance to NRTIs.

Monotherapy – For monotherapy to succeed as HAART, the agent has to be very potent yet tolerable. Kaletra, boosted DRV, and DTG monotherapy have all failed as maintenance treatment. In all likelihood, a mono-HAART regimen does not exist with the currently available antiretrovirals. Furthermore, the availability of fixed dose combinations has now simplified dosing to such an extent that monotherapy is less appealing than it used to be.

Induction-maintenance therapy – the concept of using HAART as induction to be followed by less potent regimens such as double nucleosides is attractive, but is not supported by evidence. Failure is almost inevitable in clinical trials. However, as the newer antiretrovirals have become more potent and less toxic, there is renewed interest in this approach. Strictly speaking, switching from three drugs to the abovementioned 2-drug maintenance regimens is a variation of the induction-maintenance approach. The combination of injectable cabotegravir and RPV is now being studied as a maintenance regimen after successful induction with three drugs for 20-24 weeks.

Goals of therapy

In clinical practice, the goals of HAART are three-fold:

- suppression of viral replication to undetectable levels for as long as possible,
- immune reconstitution as manifested principally by a rise of CD4 count, and
- reduction of morbidity and mortality.

Durable suppression of viral load

Durable suppression of viral load is the desired outcome. Although partial suppression may also be beneficial in immunologic and clinical terms, this is not acceptable as a treatment goal unless no reasonably effective HAART can be constructed, e.g. in the case of multiple resistance. Fortunately, the availability of a diverse arsenal of antiretrovirals has rendered this scenario uncommon.

Viral load is the concentration of RNA in plasma as measured by reverse transcription polymerase chain reaction (RT-PCR), branched DNA (bDNA) or Nucleic Acid Sequence Based Amplification (NASBA). It is preferable to follow a patient with the same testing method as results may differ. Patients on HAART should attain suppression of their plasma viral load to below the limit of quantitation. This limit varies with the particular testing methodology and its version. For clinical use, a detection limit of 50 to 75 copies /ml is sufficient.

Immune reconstitution

In general, immune reconstitution follows the use of HAART and successful suppression of viral load. There is a biphasic increase of CD4 T lymphocytes, where the first rapid wave of increase is represented by mainly memory (CD45RO+) cells, followed a few months later by the addition of naïve (CD45RA+) cells. Proliferative lymphocyte responses to recall antigens and mitogens are increased over time. There is reduced T cell activation due to reduced viral replication. The T cell receptor repertoire is also partially restored. However, immune response specific to HIV antigens remains weak.

Clinically, immune reconstitution is evidenced by the spontaneous remission or improvement of some opportunistic infections. Primary and secondary prophylaxis can be safely stopped upon immune recovery. In this process, however, IRIS may also occur.

Reduction of morbidity and mortality

HAART has had dramatic impact on the overall mortality and morbidity of HIV infected patients. In Hong Kong, median survival after AIDS increased from 29.8 months during the pre-HAART era to >70 months during the HAART era. Use of HAART *per se* resulted in an 80-91% reduction in AIDS or death in those with advanced disease.[11] At the individual level, immune recovery has made it possible to treat many otherwise crippling opportunistic diseases, e.g. cryptosporidiosis, microsporidiosis, Kaposi's sarcoma, and progressive multifocal leukoencephalopathy. As a group, the life expectancy of HIV infected patients who are diagnosed early and achieve durable viral suppression is almost the same as that of persons without HIV.

Monitoring of treatment

Clinical evaluation

The patient should be seen more frequently in the initial period of treatment. Adverse effects of medications are usually more severe and frequent in this stage. The physician should proactively manage such adverse effects. Diarrhoea with PI might be controlled by a high fibre diet, Metamucil, calcium tablets or imodium. Patients should be forewarned to return to the clinic immediately when hypersensitivity reactions occur with NVP and ABC.

On the other hand, IRIS is common with certain infections, such as mycobacteria, CMV, *Pneumocystis jirovecii* and other fungal infections. Presentations are typically atypical and require great clinical acumen for diagnosis and differentiation from treatment failure.

Viral load and CD4 count

Immediate response to treatment is assessed by viral load (VL). Effective treatment should decrease the VL by at least 2 logs within 8 weeks and achieve an undetectable VL within 6 months. The viral decay is even more rapid with INSTI-based treatment. Failure to reach these milestones should prompt an immediate evaluation to exclude non-adherence, unfavourable drug interactions, drug malabsorption and superimposed infections or vaccination.

VL will remain undetectable as long as HAART is successful. In the absence of significant replication, development of resistance is virtually nil. However, 'viral blips' infrequently occur. These are intermittent episodes of detectable low-level viremia, usually <500-1000/ml, which resolve spontaneously by returning to undetectable levels without a change of therapy. They are likely due to laboratory variation or viral release from latently infected cells. The challenge is to differentiate from early virolgoic failure and inadequate adherence. The distinction is important as viral blip is not associated with viral resistance. Of note, intercurrent illness and vaccinations do not cause viral blips in patients on effective HAART, although the CD4 count may be temporarily depressed.

The current standard of care also demands pre- and post-treatment CD4 for monitoring. Pre-treatment CD4 indicates the need of additional chemoprophylactic treatment, and post-treatment rise in CD4 assures an improved prognosis. It is noted that the lower the nadir CD4 count, the more limited is the eventual recovery and it is uncommon for it to return to pre-infection levels. Aside from clinical

conditions, the CD4 count is the most important laboratory marker for initiating and stopping prophylactic therapy.

As the patient continues to show an undetectable VL and a consistently high CD4 count, the frequency of monitoring can gradually relax to every 6 months and 12 months respectively.

Biochemical and haematologic monitoring

The range of antiretroviral toxicity is diverse. For example, the haematologic profile is monitored for toxicity of ZDV. Liver function tests are necessary for treatment with PI and NVP, and for those coinfected with hepatitis B or C. Renal function tests and periodic urine for protein/creatinine ratio are indicated with TDF, especially when given in combination with ddI and PI. Cholesterol profile and fasting sugar before and after treatment is also advisable. Most clinics undertake biochemical and haematologic monitoring for patients on treatment at least quarterly. This can be relaxed if the patient has been stabilised for a long time on a therapy without untoward effects.

Mitochondrial toxicity may occur with all NRTIs. Severe toxicity to the extent of lactic acidosis is mainly limited to the now obsolete d4T, ddI, and zalcitabine, although ZDV may also be culpable. Features may include nausea and vomiting, dyspnoea, fatigue, weight loss, and hepatomegaly, with or without severe neuromuscular weakness. Where symptoms and signs are consistent, a venous lactate >5 mmol/dL, an elevated anion gap and abnormal liver function tests are diagnostic.

Resistance testing

It is not necessarily true that the viral population in the treatment-naïve consists solely of wild type. Patients who contracted the infection in countries where antiretrovirals were in use have a higher chance of harbouring primary, transmitted drug resistance. Although wild type virus is expected to eventually overgrow resistant viruses because of a difference in replicative fitness, this process of revertant mutations takes a relatively long time to complete.

Resistance testing should be performed in all patients as soon as possible after diagnosis to aid in the design of HAART. Resistance testing is also necessary when decrease in viral load is suboptimal following initiation of treatment, or viral load rebounds above 500/ml after initial suppression. The identification of mutations will guide the formulation of alternative therapy.

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) may be useful in the monitoring of patients on ART other than NRTI. Although antiretrovirals are commonly prescribed in standard dosage, it is known that considerable inter- and intra-individual variations in drug levels occur. Furthermore, drug exposure is correlated with treatment success and toxicities. However, for want of a valid and well defined reference range, and a convenient pharmacokinetic parameter, the use of TDM is currently limited to individual case for evaluation of DDI and adherence.

Other considerations in the use of HAART

Treatment for prevention

Viral suppression effectively prevents sexual transmission of HIV. This idea has grown from a theory to a fact supported by multiple studies, and has special importance to those patients who have serodiscordant partners. At a community level, viral suppression of most patients will also lead to reduced transmission and potentially reversal of the HIV epidemic. That 'undetectable equals untransmittable' should also be a message propagated wide into society, as much of the stigma attached to persons with HIV arose from fear of infection.

Pre-exposure prophylaxis (PrEP)

Success has been shown with daily or on-demand FTC+TDF in men who have sex with men and partners of HIV infected patients. A TDF-impregnated vaginal gel also works for women. Adherence is the key for success. Research is ongoing with other drugs and novel ways of administration, such as injectables, rectal gel and vaginal ring.

It cannot be overemphasised that, if antiretrovirals were given as PrEP, the standard of care required should be no lesser than those with established HIV infection. This applies to monitoring of toxicity, enforcement of adherence, and behavioural risk reduction. In particular, frequent monitoring is necessary for breakthrough HIV infection and acquired resistance.

Interruption of therapy

Although treatment interruption as a strategy of treatment is inadvisable, HAART may be interrupted when a patient undergoes surgery, develops intercurrent illness or manifests significant toxicity. All interruptions and subsequent resumption should preferably be supervised, as there are risks involved. For example, after stopping an NNRTI-regimen, the prolonged half-lives of NNRTI will maintain their concentrations above the IC_{95} level for up to 3 weeks, greatly increasing the chance of resistance. Stopping hepatitis B-active antiretrovirals in a patient co-infected with hepatitis B may also result in flare of hepatitis. Viral rebound upon discontinuation of therapy has been reported to result in the acute retroviral syndrome.

Convenience and tolerability

Currently all antiretrovirals require no more than twice a day dosing, taking advantage of inherent favourable pharmacokinetics or pharmacokinetic boosting. Fixed dose combination pills further simplifies treatment. Up to eight single tablet regimens are now available, all of which comprise three drugs in one tablet and need to be taken only once a day. Indeed, treatment simplification is now the most common reason for switching therapy. However, it must be emphasised that there are considerable individual variations in tolerability and acceptance. What the provider views as simplified treatment may be viewed with scepticism by patients who are used to their multi-drug treatment. Co-morbidity and life style requirements can make otherwise 'recommended' regimens unsuitable. An individualised approach therefore always takes precedence.

Cost

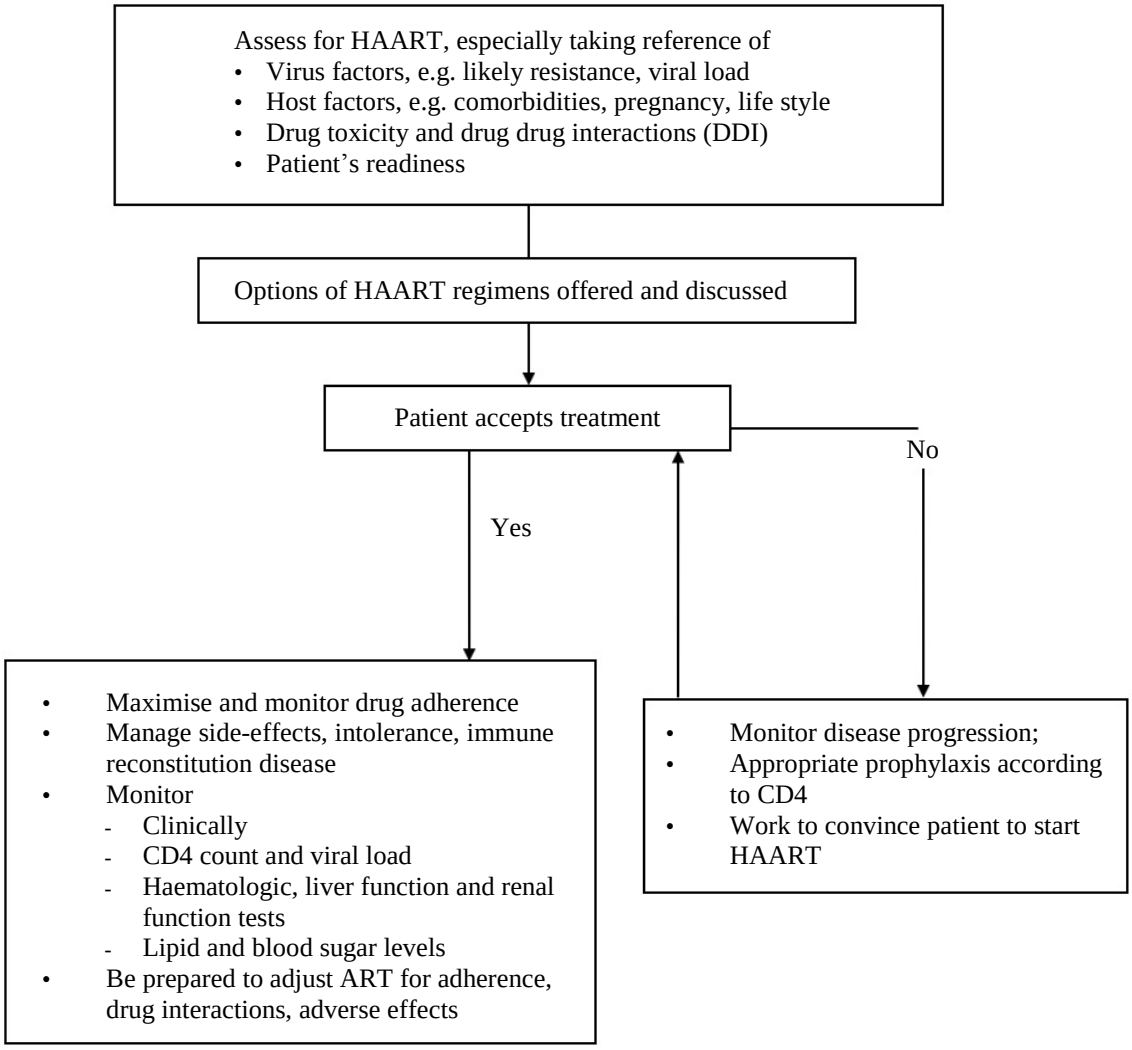
HIV infection has become the costliest disease to treat. In Hong Kong, drugs alone average HK$100,000 per year for a patient. As of now, the number of drugs with expired patents is small. At any rate, they are mostly obsolete, having been supplanted by newer drugs in terms of tolerability, convenience or effectiveness. In developed countries, the generic alternatives may not be significantly cheaper either.

There is no denying the huge benefits of antiretrovirals. However, as life expectancy improves and the number of patients grows, financial constraints are beginning to show. To sustain the success Hong Kong has enjoyed in the HAART era, continuing commitment is crucial. WHO has clearly defined the target of a 90-90-90 cascade of care. What this means is that by 2020, 90% of people with HIV should have been diagnosed, 90% of the diagnosed should have been put on treatment, and 90% of the treated patients achieved viral suppression. Policy makers and budget holders have to be convinced that effective treatment with broad coverage also prevents infections and is key to controlling the HIV epidemic.

Box. List of antiretrovirals available or expected soon in Hong Kong

Drug	Dosage
Nucleoside reverse transcriptase inhibitor	
Zidovudine (AZT, ZDV, Retrovir®)	250 mg bid, 300 mg bid
Lamivudine (3TC, Epivir®)	150 mg bid; 300 mg qd
Abacavir (ABC, Ziagen®)	300 mg bid; 600 mg qd
Tenofovir (TDF, Viread®)	300 mg qd
Non-nucleoside reverse transcriptase inhibitor	
Nevirapine (NVP, Viramune®)	200 mg bid, 400mg qd (NVP-XR); 200 mg qd in first 2 wk
Efavirenz (EFV, Stocrin®)	600 mg nocte; 400 mg nocte as alternative
Etravirine (ETR, Intelence®)	200 mg bid; 400 mg qd (for initial therapy)
Rilpivirine (RPV, Edurant®)	25 mg qd
Protease inhibitor	
Darunavir (DRV, Prezista®)	800 mg qd + RTV 100 mg qd; 600 mg bid + RTV 100 mg bid
Atazanavir (ATV, Reyataz®)	400 mg qd; 300 mg qd when boosted with RTV 100 mg
Kaletra® tablet (Lopinavir 200 mg/RTV 50 mg); half-strength tablet (lopinavir 100 mg/RTV 25 mg)	2 tablets bid; 4 tablets qd For women in 3rd trimester: 3 tablets bid, or 2 full-strength + 1 half-strength tablet bid
Integrase inhibitor	
Raltegravir (RAL, Isentress®)	400 mg bid; 1200 mg qd
dolutegravir (DTG, Tivicay®)	50 mg qd; 50 mg bid for partial resistance
CCR5 inhibitor	
Maraviroc (MVC, Selzentry®)	300 mg bid
2-drug fixed dose combination	***Composition***
Combivir®	AZT 300 mg +3TC 150 mg; bid
Kivexa®	ABC 600 mg + 3TC 300 mg; qd
Truvada®	TDF 300 mg + FTC 200 mg; qd
Descovy®	TAF 10 mg or 25 mg + FTC 200 mg; qd
Prezcobix®	DRV 800 mg + Cobicistat (COBI) 150 mg; qd
Juluca®	DTG 50 mg + RPV 25 mg; qd
3-drug single tablet regimen (all once daily)	
Atripla®	TDF + FTC + EFV
Complera®	TDF + FTC + RPV
Odefsey®	TAF + FTC + RPV
Bictarvy®	TAF + FTC + bictegravir (BIC)
Triumeq®	ABC + 3TC + DTG
Genvoya®	TAF + FTC + elvitegravir (EVG) + COBI
Symtuza®	TAF + FTC + DRV + COBI
Delstrigo®	TDF + 3TC + doravirine (DOR)

Algorithm. Initiating and following antiretroviral therapy for treatment-naïve patients with established HIV infection



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Test paper - **Overview of antiretroviral therapy in 2019**

Expiration Date: 28 April 2020

CME point [#] ***/ CNE point: 1 / PEM point: 0 (Midwifery related)***

- Please choose the best option.
- Answer these on the answer sheet and make submission by fax to Special Preventive Programme, Department of Health.

 # Please contact respective authorities directly for CME/CPD accreditation if it is not on listed below.

Accreditors	CME Point
Department of Health *(for practising doctors who are not taking CME programme for specialists)*	1
Anaesthesiologists	1
Community Medicine	1
Dental Surgeons	1
Emergency Medicine	1
Family Physicians	1
Obstetricians and Gynaecologists	pending
Ophthalmologists	1
Orthopaedic Surgeons	0
Otorhinolaryngologists	pending
Paediatricians	1
Pathologists	1
Physicians	1
Psychiatrists	1
Radiologists	1
Surgeons	1

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1. Which of the following best defines 'highly active antiretroviral therapy' (HAART)?

   (a) HAART is the use of two or more antiretrovirals in combination
   (b) HAART refers to antiretroviral therapy that results in durable suppression of viral load to undetectable levels
   (c) Antiretroviral therapy is HAART is if results in sustained rise in the CD4 count
   (d) Antiretroviral therapy is HAART only if it comprises a double nucleoside backbone in addition to a protease inhibitor, an integrase inhibitor or a non-nucleoside reverse transcriptase inhibitor
   (e) None of the above

2. In which of the following situations should HAART be withheld?

   (a) An asymptomatic patient with CD4 580/uL
   (b) A patient with recent history of zoster involving T4 and T5 dermatomes but a current CD4 count of 650/uL
   (c) A patient with acute HIV infection
   (d) A patient with newly diagnosed cryptococcal meningitis and a CD4 count of 10/uL
   (e) A patient with cervical TB lymphadenitis and a CD4 count of 45/uL

3. Which of the following is an appropriate strategy of using HAART?

   (a) HAART should not be initiated in a person who habitually uses heroin until he is put on methadone maintenance
   (b) An alternating strategy of two HAART regimens with different resistance profiles enhances the prospect of long term viral suppression
   (c) When diagnosed, TB meningitis necessitates immediate use of HAART
   (d) HAART is indicated for treatment of progressive multifocal leukoencephalopathy
   (e) All of the above

4. Which of the following is not a known benefit of antiretrovirals?

   (a) prevention of onward HIV transmission by shared needle use
   (b) prevention of mother-to-child transmission of HIV
   (c) reduction of morbidity and mortality
   (d) prevention of HIV acquisition by HIV-uninfected individuals
   (e) immune reconstitution after initiation of antiretroviral treatment

5. Which of the following associations is NOT appropriate?

   (a) transmitted drug resistance and nevirapine
   (b) low genetic barrier and raltegravir
   (c) dizziness and efavirenz
   (d) mitochondrial toxicity and stavudine
   (e) All are appropriate associations

6. Which of the following treatment strategies will likely prevent emergence of primary antiretroviral resistance in the community?

   (a) maintaining treatment adherence at >95%
   (b) rapid initiation of nevirapine-based HAART on the day of confirmed HIV diagnosis
   (c) Alternating regimen of NNRTI- and PI-based HAART
   (d) a + b
   (e) a + c

7. Which of the following statements regarding the monitoring tools of antiretroviral treatment is false?

   (a) baseline resistance assay should be performed for all patients
   (b) screening for dual and X4 tropic viruses is necessary before use of maraviroc
   (c) therapeutic drug monitoring should be considered when complex drug drug interactions are anticipated
   (d) CD4 count has to be measured at least 6-monthly for all patients
   (e) none of the above

8. Which of the following treatment considerations is appropriate?

   (a) Your patient is on Truvada + efavirenz, currently tolerating his treatment well and with undetectable viral load. However, a test report shows that he has a CYP2B6 polymorphism which predisposes to CNS adverse effects of efavirenz. You recommend decreasing the dose of efavirenz to 400 mg daily.
   (b) Your patient is on Genvoya, currently tolerating his treatment well and with undetectable viral load. However, he has lately been missing his appointments. Although he denies it, you suspect he is not fully adhering to his treatment. You therefore withhold treatment for the time being

(c) Your patient is on Truvada + dolutegravir, currently tolerating her treatment well and with undetectable viral load. Having discussed with her husband, she expresses to you her desire to conceive. You recommend changing to Combivir + dolutegravir because of the well known effectiveness of zidovudine in preventing mother to child transmission.
(d) Your patient was put on Kivexa + efavirenz two weeks ago. She returns today with fever and severe rash. You decide to stop all antiretroviral treatment immediately and plan on restarting with Triumeq when the symptoms subside.
(e) None of the above

9. Which of the following regarding using only one or two drugs for HIV treatment is true?

(a) A few two-drug regimens have shown success as maintenance therapy for those who have achieved prolonged viral suppression with conventional treatment
(b) For treatment naïve patients with viral load <100,000/uL, dolutegravir monotherapy is as effective as conventional three-drug regimens
(c) All successful two-drug regimens have dolutegravir as the common component
(d) No two-drug regimen has shown success as initial treatment in randomised clinical trials
(e) none of the above

10. Which of the following is reasonable expectation of antiretroviral therapy in the future?

(a) Long acting formulation of treatment that does not require daily dosing will become available
(b) Two-drug regimens may become acceptable as initial treatment
(c) Wide treatment coverage of patients will decrease the incidence of new infections.
(d) New class of antiretrovirals will emerge
(e) All of the above