



ART failure and strategies for switching ART regimens in the WHO European Region

Report of the WHO expert consultation

Copenhagen, 7 December 2007



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Abbreviations

½ T	half time
3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
AZT	azidothymidine
d4T	stavudine
ddI	didanosine
DR	drug resistant
EACS	European AIDS Clinical Society
EFV	efavirenz
ESLD	end-stage liver disease
ETV	entecavir
FDC	fixed-dose combination
HAART	highly active antiretroviral therapy
HBe	hemoglobin e
HBeAG	hepatitis B antigen
HBsAG	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IDU	injecting drug user
LAM	lactational amenorrhea
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MDR TB	multi drug resistant tuberculosis
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PI	protease inhibitor
PK	peak concentration
PLHIV	people living with HIV
RNA	ribonucleic acid
RTV	ritonavir
TAM	thymidine analogue mutation
TB	tuberculosis
TDF	tenofovir
TDM	therapeutic drug monitoring
VL	viral load
XDRTB	extensively drug resistant tuberculosis
ZDV	zidovudine (also known as azidothymidine (AZT))

Introduction and background

The introduction of highly active antiretroviral therapy (HAART) represents a major turning point in response to the HIV/AIDS epidemic. After more than ten years of use, HAART treatment's effect has been documented in all WHO European Region countries reporting, as increased survival, decreased HIV associated mortality and vastly improved quality of life. An infectious disease with an almost universally fatal outcome has been transformed into a manageable chronic infectious disease. Regional countries have made significant progress towards universal access to antiretroviral therapy (ART). By the end of 2002 around 242 000 patients were receiving HAART in the European Region, including 7000 in central and eastern Europe (1). By the end of 2007 about 435 000 were on ART in Europe, including 55 000 in central and eastern Europe (2). By mid-2007, HAART was available in the public sector health services in every country of the Region except Turkmenistan, with coverage estimated as very high (more than 75% of those in need of treatment) in at least 38 out of 53 Member States (2).

Health care system infrastructures, human and financial resources, availability and affordability of a range of antiretroviral drugs (ARVs) and modern medical technologies including both CD4 estimation and HIV viral load determination characterize most Region countries. Viral load measurement (VL) is widely used for monitoring ART response and to determine the optimal time for switching to a second-line regimen. The role of HIV drug resistant (DR) testing in the decision to switch ART regimens remains less clear. To most effectively and efficiently utilize resources while maximizing health outcomes, this needs to be considered in a public health approach, in light of the prevalence in the Region. Comorbidity of HIV and hepatitis C and B infections also needs to be taken into account.

VL measurement can assess adherence and document ART success by demonstrating suppression of HIV replication, and diagnose treatment failure early. Early recognition of treatment failure allows switching regimens at a time when few thymidine analogue mutations (TAMs) have accumulated, thus improving the likelihood that nucleoside or nucleotide reverse transcriptase inhibitor (NRTIs) will maintain their activity in any second-line regimen.

Definitions of early and late switching are not well established. Switching ART based only on immunological and clinical evidence of a lack of ART effect may be associated with greater accumulation of TAMs, and thereby reduce the activity of NRTIs recommended by WHO for second-line ART: abacavir (ABC), didanosine (ddI), tenofovir (TDF). It is currently unclear what impact this may have on the widespread emergence or transmission of DR virus at the population level. VL testing may not be an efficient or effective use of public health resources if used too frequently or to precipitate switching to a second-line therapy in the absence of real loss of viral suppressive activity of a first-line regimen.

There is at present a lack of consensus on early and late ART treatment failure, and on the VL threshold level defining first-line treatment failure that leads to a decision to switch to a second-line regimen.

Objectives

The meeting had the following objectives:

- to review existing evidence for use of virological, immunological and other tests as well as clinical endpoints in monitoring ART response;
- to review national ART recommendations and goals in western Europe and consider definitions of ART failure in a public health approach (first- and second-line ART and when to switch);
- to examine HIV/AIDS national programmes' capacity to utilize VL and CD4 measurement; and
- to review the role of HIV comorbidity with hepatitis C and hepatitis B at the VL threshold level constituting first-line ART failure in coinfecting patients.

Expected outcomes

- Regional working definitions of the goal of ART and ART failure (early and late);
- recommendations on the use of VL, CD4, DR and therapeutic drug monitoring (TDM) measurements in a public health approach for European countries; and
- recommendations on a strategy for switching to second-line ART and switching to salvage options.

Target audience

Regional HIV/AIDS experts involved in the development of national recommendations on HIV/AIDS treatment and care, experts on laboratory technologies and WHO staff.

Opening

Dr. Srđan Matic, WHO Regional Adviser on HIV/AIDS and Sexually Transmitted Infections, welcomed participants on behalf of the Regional Office for Europe, emphasizing the importance of the meeting for the Region in pushing forward technical guidance for treatment and care from the basic framework developed by WHO at the global level to a more regionally specific context.

There are basically three possible outcomes when monitoring the success of treatment and determining which strategy to use when switching ARV regimens: clinical, immunological and virological. A great deal of discussion has been devoted to defining virological failure and in establishing consensus at what point it occurs and its implications. It is important for WHO, as a public health agency, to develop recommendations based on the best available evidence and to make practical recommendations to Member States on patient management, health service organization and drug procurement while considering financing and sustainability. Clinical recommendations also have significant implications in countries that are still struggling with basic health issues. Because the WHO European Region enjoys health care infrastructures with developed human resources and laboratory capacities for monitoring populations and treatment outcomes, it can go beyond the global recommendations.

Treatment failure and switching regimens could not be addressed clearly and precisely when the HIV/AIDS clinical protocols for the Region were developed. It is expected that this meeting will rectify this issue, while contributing to the WHO global meeting in Geneva in February 2008.

Summary of presentations and discussions

Public health and ART

Progress on universal access to ART

The goal of the “3 by 5” initiative was to ensure access to ART as a basic human right to health, irrespective of national socio-economic conditions. The initiative was a bit late (end of 2007) in reaching the target of three million people on treatment, but the intention of the goal was achieved in the G8 summit in Glenn Eagles, when donor agencies committed to universal treatment. Globally, more than 30% of those in need of treatment are now receiving it. Progress is being sustained globally, as treatment is now accessible in capital cities as well as elsewhere in countries.

WHO global public health approach to ART

The WHO’s global vision for treatment is first and foremost to extend life, and then to have one evidence-based global standard for ART. This is particularly important in low income settings, and consists of:

- one first-line then one second-line regimen (then stop or salvage)
- sequential use of three oral drug classes
- simple recommendations for switch timing and toxicity substitutions
- consideration of the availability of and access to laboratory monitoring and
- standard population-based HIVDR monitoring and surveillance.

The process being adopted is evidence-based, while simplifying and standardizing treatment.

Simplifying and standardizing key ART clinical management issues

The WHO global definitions of first and second-line ART are:

First-line ART: the initial regimen prescribed for patients fulfilling national clinical and laboratory criteria for starting ART. Current WHO treatment guidelines recommend two NRTIs and one NNRTI for initial treatment.

Second-line ART: is the regimen used immediately after first-line therapy has failed (clinically, immunologically or virologically). Current WHO treatment guidelines recommend that the PI class be reserved for second-line ART, preferring ritonavir-boosted protease inhibitors (bPIs) supported by two agents from the NRTI class.

One of the major opportunities that has come from focusing on a small number of first-line medications has been major price reductions. Manufacturers of both brand-name and generic medicines have been able to focus on a few products, fixed-dose combinations (FDC) in particular; consequently, there has been significant price competition and market consolidation

around these few regimens, resulting in impressive price reductions. The first-line standard FDC of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) is now available for as little as \$91 a year.

This has not been the case with second-line ARVs. There is a much wider variety of second-line regimens in use – about 30 in middle-income countries, according to a recent WHO survey.

A critical issue, therefore, is that the choice of first-line regimens has a significant impact on second-line choices. The first-line choices come down to a thymidine analogue, d4T or azidothymidine (AZT), and a NNRTI component, and for second-line two new NRTIs and the introduction of a PI, preferably ritonavir boosted. Consensus is that the PI should be boosted lopinavir (LPV) or boosted atazanavir (ATV) in heat stable combinations, with ritonavir (RTV) alone as a heat stable compound.

If therapy is started with d4T and 3TC then the urgent first-line backbone to support the boosted PI would be TDF or ABC combined with 3TC or ddI. However, there was considerable discussion of what the exact NRTI component would be when there is likely to be significant resistance acquired in patients whose treatment is failing.

There are similar issues if the first-line regimen is a non-thymidine analogue, i.e. using TDF or ABC. There is the same prioritization for the boosted PI but with a slightly different NRTI component.

The key issues in ART clinical management decisions are when to:

- start ART
- substitute for toxicity or drug-drug interactions (alternative first-line)
- switch from first-line due to failure
- use salvage with second-line failure
- stop second/third-line due to failure.

In the public health sector there is no provision for any third-line or salvage regimens at present. The Global Fund has not been approached about this, and it is not included in PEPFAR programmes considering which drugs to use after failed second-line therapy. The main challenge at the moment is to increase the procurement and availability of second-line drugs and PIs. There is debate about whether third-line or salvage regimens should be included in the public health approach.

Failure and switching

Initiating ART is best guided by clinical symptoms or evidence of immunodeficiency by measuring CD4 counts. The purpose of the clinical staging is to train staff at low-level centres to identify when patients need to be referred to centres that decide on treatment initiation or modification when ARVs are failing. Clinical staging for initiation of ART enables millions of patients to access therapy where CD4 is not available.

Failure is far more difficult. Both early and late switching, from the time ART no longer suppresses the virus to the maximum extent, have advantages and disadvantages. An early switch

can preserve treatment options and the patient's ability to effectively respond to second-line ARVs therapy. A late switch allows more patients to stay on first-line therapy, keeping medicine and laboratory monitoring costs down. Moreover, many people only have access to first-line ARVs because of limited availability to second-line drugs. The disadvantages of a late switch are the increased risk of accumulating drug resistance and mutations, resulting in fewer choices of active ARVs for second-line therapy. A late switch also increases the possibility of a poor response to the new therapy because the patient may be too ill.

There are three different definitions for failure: clinical, immunological and virological. The WHO 2006 global guidelines (3) define:

- *clinical failure* when there is a new or recurrent WHO stage 4 condition;
- *immunological failure* when CD4 falls to the pre-therapy baseline (or below) or there is a 50% fall from the on-treatment peak value (if known) or CD4 levels are persistently < 100 cells/mm³; and
- *virological failure* when plasma VL $> 10\,000$ copies/ml.

The consensus expert opinion of virological failure of $> 10\,000$ copies/ml is not an evidence-based recommendation as no data currently exists to make a formal recommendation. The PLATO study suggests that as long as VL continuously remains $< 10\,000$ copies/ml, CD4 cell gains can be expected (4).

It is clear that if the initial goal of treatment is to maximally suppress viral replication, then failure is defined by this goal not being achieved; therefore, failure occurs when virus is detectable at least 6 months after ART has been initiated (upon confirmation that lack of adherence is not a factor). There are patients for whom maximum suppression cannot be achieved due to three-class drug resistance. In such circumstances the goal then becomes maintaining VL at its lowest possible levels.

Discussion

There is a need to look carefully and closely at the lessons learnt from standardizing treatment approaches such as in the TB and malaria programmes, which contributed to the appearance of multi-drug resistant TB (MDR TB) and extensively drug resistant TB (XDR TB). WHO has a responsibility to indicate to Member States what is possible. The criterion should not be just what governments are presently able to deliver, but what could be better for patients within their capacities. The "3 by 5" initiative, in getting treatment to three million people by 2005, is an example of WHO standing up for something that everyone said was impossible.

Recommendations that are meant for all settings may appear to be minimal. The approach that needs to be taken is one in which countries not satisfied with the minimal recommendations strive to achieve the optimal ones. Recommendations can be made so that higher targets are attainable, pushing countries towards improved standards of care, rather than creating standards that are below what is already achievable for most countries in the WHO European Region. Cost effectiveness, implementation of laboratory monitoring and planning all need to be considered as the epidemic spreads.

The decision for an early or late switch depends on the availability of second-line and salvage regimens. If salvage is not available in the public sector, then there is a strong imperative to

make the second-line regimen work maximally, meaning that late switching should be favoured if a very potent second-line regimen is available and a third-line regimen is not. Arguments for early switching become stronger if three regimens are available.

WHO Geneva will be addressing guidelines for third-line regimens over the next few years, in particular with regard to integrase inhibitors. Recommendations will to some degree depend on funding mechanisms. The fact is that second-line treatment is already available.

ART guidelines and capacities

ART goals and failure and management strategy

All guidelines¹ reviewed define the goal of ART in virological terms, namely, undetectable VL after 3–6 months of treatment and maintaining this level thereafter. This is based on evidence from France, Italy and Sweden. An intermediate goal of a 1 or 2 log₁₀ decrease or achieving 1000 copies/ml (5) after 4 or 8 weeks of ART was also included by five countries. The European AIDS Clinical Society (EACS) also formulated the goal according to virological failure (6).

While the goal of ART is defined similarly in all the reviewed guidelines, failure is described differently. While ART failure is not necessarily formulated in the guidelines, all but the French equate virological failure with ART failure. The French guidelines do say that persistence of VL > 500 copies/ml exposes patients to viral accumulation of resistant mutations that compromise future therapeutic options (7). The German-Austrian and Swedish guidelines also include immunological and clinical failures (8, 9).

All guidelines use VL criterion as the key indicator in switching the ART regimen, but their endpoints differ. Physicians also differ in their strategies for suspected ART failure. All guidelines recommend HIV DR testing for all patients in this context.

HIV treatment and care services in eastern Europe and central Asia

HIV/AIDS treatment and care services in these countries are provided exclusively by the public health systems, which have in general only been administering ART since 2003 or 2004. Seven of twelve countries (excluding the Baltic states) – Armenia, Azerbaijan, Georgia, Belarus, Kyrgyzstan, Tajikistan and Uzbekistan – have fewer than 100 diagnosed HIV cases per million population, and the remaining four countries – Kazakhstan, Moldova, the Russian Federation and Ukraine) have between 100 and 288 HIV cases per million population. Epidemics are concentrated mostly among IDUs and their sexual partners (10).

HIV treatment and care services for out-patients are provided in eastern European countries through AIDS centres or polyclinics exist in practically every city. In-patients are either referred to infectious disease hospitals or infectious disease units in general hospitals. Treatment and care for both in and out-patients are provided either by multidisciplinary teams or at the least by physician-infectionists. Specialized HIV services work as primary health care facilities (no referral needed, no waiting list, services free of charge). There is no lack of physicians, but there

¹ In addition to the guidelines previously or subsequently mentioned, other guidelines include: Spanish guidelines (Recomendaciones de GESIDA/Plan Nacional sobre el Sida respecto al tratamiento antiretroviral en adultos infectados por el virus de la inmunodeficiencia humana, *Enfermedades Infecciosas y Microbiología Clínica*, 2007; 25 (1):32–53) and Italian guidelines (Aggiornamento delle conoscenze sulla terapia dell'infezione da HIV, Ministry of Health, Rome, 2007).

may be a lack of capacity (examples: Yerevan, Armenia: 4 doctors for 170 patients; Vinnitsa, Ukraine: 24 physicians – including infectious disease specialists, gynaecologists, psychiatrists, dentists and others – in an AIDS centre for 1000 patients, and in Crimea, there are 24 physicians for 7000 HIV patients) (11).

Once HIV diagnosis is confirmed, territorial AIDS centres register PLHIV, who then become eligible for continuous treatment and care free of charge. From 6–30% of PLHIV under care are presently on ART (10). This wide range is due to not all PLHIV needing ART at a given time: some are preparing for treatment and others may be eligible but not receiving it because they are active IDUs. This latter group still does not have good access to treatment and care or other supportive services; it is unclear how many active IDUs go for care.

All the countries have regular, free CD4 testing available for PLHIV. VL testing is available in most of the countries except Kyrgyzstan, Tajikistan and Uzbekistan, which are looking for opportunities to procure polymerase chain reaction (PCR) machines to undertake this testing. Countries that do have the capability perform VL tests regularly (11). Though WHO does not recommend HIV DR testing on an individual basis, three countries (Belarus, Georgia and the Russian Federation) have started testing patients who fail ART regimens (11).

Defining ART failure

Six of the eleven countries use both VL and CD4 criteria in determining ART failure. Four countries in central Asia use only CD4 count; three of them do not have VL equipment, and one has not yet had been faced with the situation (11). The time of ART failure based on VL criterion varies from 24–48 weeks with the VL end-point value of 50–500 copies/ml. Seven of the ten countries faced with the scenario switch as soon as ART failure is determined (11).

ARV availability

All countries have NRTIs, NNRTIs and a range of PIs recommended by WHO; only Kyrgyzstan and Tajikistan are limited to LPV/r. Two countries have fusion inhibitors (Georgia and the Russian Federation). All countries providing ART follow WHO recommendations for first-line regimens. The two most common first-line regimens used:

- ZDV + 3TC + (EFV or NVP)
- d4T + 3TC + NVP (3 of 8 countries: Azerbaijan, Moldova, Tajikistan)

In Ukraine, ART is administered with boosted PIs, in particularly Kaletra is very popular.

Approaches to patient management

There are two classical approaches to patient management, focused on either the individual patient or on public health. The latter is understood to mean that large numbers of people are in need of ART and there are limited resources (financial, technical, human and infrastructural), at times meaning less than optimal care. There may also be a reduced number of treatment and monitoring options, which helps to reduce the cost. Countries in this region fall between these two approaches. They are looking to optimize care of individual patients, and utilizing resources is less of an issue as the number of people in need of treatment is actually manageable. The WHO Regional Office assists countries in using their resources efficiently. The public health approach allows building on the best practices with efficient utilization of resources.

Discussion

WHO/UNAIDS estimates of the number of PLHIV and those in need of treatment in the Region may be too high. Physicians at times do not see patients seeking treatment and care for HIV in numbers reflective of the estimates. The WHO Regional Office will address the estimation issues with countries in the coming biennium.

A significant proportion of people testing positive are followed up by the medical system. Most countries fall in to the range of low-level or concentrated epidemics, with limited numbers of PLHIV. The only countries with health system issues are Ukraine and the Russian Federation, because of the more significant burden of disease and the higher concentration of PLHIV in specific cities or regions.

Countries may have interpreted questions on the availability of ARVs based on different assumptions: some may have meant they recommend certain drugs that should be available, regardless of whether they actually are; others may have the drugs registered but not used, and still others actually have the drugs available.

The emerging view in western Europe is that the predominant way to identify failure is virological. Other countries in the Region are also interested in introducing second-line regimens based on results of VL testing. If the VL is undetectable it is clear that the clinical and immunological failure is completely irrelevant. Clinical and immunological failure are only relevant when there is no VL testing available. The same therapy should continue. There is no evidence at all that changing therapy would make a difference in terms of CD4 count.

Current evidence

The benefits of ART in addressing AIDS' defining conditions have been well established. Evidence from the SMART study (12) and several observational studies suggest that ART may also reduce risk of several non-AIDS conditions. Non-AIDS conditions are more frequent than AIDS conditions in patients with CD4 count > 200 cells/mm³. Non-AIDS related events are defined by CD4 and VL as well as other factors, such as hepatitis coinfection, alcohol consumption in liver failure, diabetes, hypertension in renal failure, etc. All of these may have implications for the selection of ARVs and regimens.

Goal of ART

The goal of ART is to achieve undetectable VL within six months of starting therapy; this should be maintained for the rest of the patient's life. In western Europe, the proportion of ART patients achieving undetectable VL ranges from 50–90% (13).

Evidence shows that ART assists patients in raising CD4 counts and decreasing VL, and if VL is kept undetectable, then CD4 counts continue to increase over the years. Factors possibly explaining the benefits of ARV for ongoing viraemia include residual antiviral activity, impairment of virus fitness and reduced virulence.

Failure and VL end-points for resistance

There are a number of predictors of drug-related mutations in virological failure: the type of drug selection pressure, the genetic composition of the virus, polymorphism and number of drug-

related mutations (inverse) already acquired, the level of replication and possibly immunological function. Future drug options are affected by the number of active drugs used in a failing regimen. Possible ARVs for future regimens become limited each time one has been part of a failed regimen or a patient cannot tolerate it. Individual patients may exhaust their treatment options quickly because of DR or to the unavailability of newer drugs.

Models project that it takes an average of five years from when first evidence of virological failure is detected until 50% of patients progress to WHO stage 3. These models also predict that DR to 3TC and NVP exist in most patients as soon as virological failure is detected, and of course if switching only occurs after WHO stage 3 has been reached. TAM mutations are only present in 25% of patients at the time of virological failure (early switch) and in 55% if the switch occurs after stage 3 (late switch).

There are many studies supporting the notion that patients kept on failing regimens accumulate more mutations than those whose regimens are switched immediately upon recognition of virological failure. This occurs irrespective of the type of regimen, provided it contains drugs with a genetic barrier higher than 1 (i.e. thymidine analogues and PIs).

Consistency of clinical and virological responses

The median interval between VL measurements of patients in western Europe is about 3 months; whereas, in eastern Europe it is from 12 to 15 months (13). The chance of virological rebound is greatest soon after commencing ART or switching it. It is more effective to have shorter intervals for VL monitoring, especially at the start of treatment. Increased duration of viral suppression is associated with lower viral rebound rates in patients with previous treatment failures.

Models are being constructed and used to predict survival rates after five or ten years, comparing early and late switching strategies (14). These models show no major difference in survival rates depending on the monitoring strategy used.

Resistance and adherence

Poor adherence leads to a lack of complete viral suppression, which in turn creates drug-related mutations. Complete interruption of ART leads to a return of pre-therapy VL levels once all drugs are cleared from the body (for some drugs, such as the NNRTIs, this may take several weeks). It is unlikely that VL levels can be used to separate partial adherence with fully susceptible virus from full adherence with resistant virus.

HIV/HCV and HIV/HBV: VL end-points for ART failure in coinfecting patients

Overview of hepatitis/HIV coinfection

Worldwide prevalence of hepatitis C (HCV) is 180 million and of hepatitis B (HBV) about 350 million. HIV infection adversely affects HCV disease. Numerous studies have shown that liver disease associated with HCV infection is accelerated in patients infected with HIV. Over a ten-year period, it has been calculated that almost seven times more coinfecting patients would be expected to develop cirrhosis than those with HCV alone (15). In addition, cirrhosis develops much faster in coinfecting patients: the mean time for HIV-negative patients is about 23 years,

and in coinfecting patients it is 6.9 years (15). Liver-related mortality in coinfecting patients has increased since ART became available, essentially because patients are not dying early from HIV infection, and are progressing to end-stage liver disease (ESLD) as they may not have been treated for hepatitis. Among HIV-infected patients in Europe, 14.5% of deaths are liver-related, and the second cause of death after AIDS-related death at 31% (16).

HIV also has a deleterious effect on HBV. In coinfecting patients there are increased carriage (HBeAg) rates and decreased seroconversion rates, greater levels of HBV viraemia, more rapid decline of antibody titres (anti-HBs), reactivation episodes, faster progression to cirrhosis, more aggressive liver cell carcinoma and increased mortality. Serum HBV-DNA predicts complications, showing that higher VLs increase chances of developing a hepatocellular carcinoma (HCC), consequently raising the possibility of developing cirrhosis.

HCV

HCV therapy is less effective in HIV coinfecting patients than in mono-infected patients. Factors associated with sustained virological response to HCV therapy may be categorized as host-related (maintaining higher CD4 cell count), viral (genotypes 2–3, baseline HCV RNA load, and undetectable HCV RNA at week 4) and treatment-related (peginterferon and weight-based ribavirin dosages, adherence and concurrent drugs). Treatment lasts 48 weeks, and the end-point is sustained virological response with negative HCV RNA detection 24 weeks after treatment withdrawal. Evidence indicates that the rate of fibrosis progression in coinfecting HCV/HIV patients is much lower if the patient is treated when the CD4 cell count is > 500 cells/mm³.

In HCV/HIV coinfecting patients it is important to assess genotype, VL and fibrosis, to use rapid virological response ($> 2 \log_{10}$ drop in HCV RNA at week 4) to better estimate the chance of sustained virological response and duration of HCV therapy, to use weight-based ribavirin, and to start therapy early, preferably before CD4 > 500 cells/mm³.

HBV

The HBV treatment goal is profound and durable suppression of HBV DNA. Evidence indicates that undetectable HBV VL decreases the possibility of having end-stage complications. Primary endpoints when treating patients with HBV are to stop or slow the progression of liver disease in order to: prevent cirrhosis, decompensation of cirrhosis and hepatocellular carcinoma. In coinfecting patients the goals of therapy are arresting or delaying liver disease progression, clearance (reduction) of serum HBV DNA, seroconversion (anti-HBe), loss of HBSAg and development of anti-HBs antibodies, reduction of liver inflammation and reduction or normalization of ALT, and reduction in the risk of transmission.

In case of ART failure, concomitant HBV DNA should be checked for, with HBV genotype and LAM resistance testing to follow if positive. If HBV has been detected at any time, tenofovir or telbivudine should be included in the new regimen.

The preferred treatments for HBV/HIV coinfecting patients are:

- if ART is not needed: Peg IFN; LdT or ADV;
- during ART: tenofovir/emtricitabine (TDF/FTC) or added entecavir (ETV) when HIV is undetectable.

HIV drug resistance testing

Drug resistance testing is recommended in all current international guidelines for HIV therapy when a failing regimen is to be switched (17–19). Resistance testing is also recommended in other clinical settings, including for newly diagnosed patients and/or patients starting therapy, pregnant women and for post-exposure prophylaxis. If HIV/DR transmission prevalence at population level is $> 5\%$ or unknown, it is cost-effective to switch without DR testing.

Evidence for resistance testing to guide treatment change

While several randomized studies show a moderate effect on treatment outcome of DR testing in failing patients (20–24),² others show no significant effect (25–27).² The drawback of these studies is that most of them are old, relatively small and may not apply to current ART or current algorithms for interpreting DR testing. A continuing problem with DR testing studies is that by the end of the study the results may no longer be applicable because of the development of new drugs, technology, or mutations/resistance.

HIV drug resistance is due to the rapid evolution of HIV-1. Resistance always develops when a patient is on monotherapy and can be prevented by three-drug combination therapy. Resistance now always develops in patients with poor adherence. Drug resistance is common among treated patients in Europe and the United States, but can usually be managed by second and third-line therapies.

Drug resistance tests

There are two main types of HIV drug resistance tests.

- Phenotypic testing is for viruses, usually recombinant, grown in the presence of drugs. It gives an IC₅₀ or fold-resistance value, and is expensive, slow and needs a BSL3 safety laboratory.
- Genotypic testing is based on clinical data and sequencing of the protease and reverse transcriptase. It checks for the presence of known resistance mutations and is preferred in most recent guidelines.

Interpreting DR testing is problematic in that mutations can occur that seem to be associated with PI resistance. There are many mutations that have complex interactions, and sophisticated, standardized tools are needed to correctly interpret the resistance testing.

Problems in testing resistance to new drugs

- Early treatment failure and problems of DR testing can occur if VL < 500 –1000 copies/ml.
- Reversion of mutations is possible following treatment discontinuation and change; resistance tests primarily score susceptibility to current therapy.
- Minority viral variants may be missed since current assays have a detection limit of 20%. An early failure or evolving resistance may not be picked up early. The clinical relevance of detecting smaller numbers of resistant virus is unknown.

² These are some examples of the mentioned studies, there are others.

- HIV DR testing is part of a consultation; it should not be used on its own, but rather should be combined with expert advice involving clinicians, virologists, pharmacologists and other relevant experts.
- Other factors should be considered when DR testing results are used to make decisions regarding next-line therapy, e.g. earlier treatment or failures, cross-resistance, side effects, drug interactions, drug levels, likely adherence, etc.

HIV drug resistance testing

Pros

- Drug resistance testing will not benefit every patient, but studies indicate that DR testing during treatment failure is cost effective.
- Algorithms and other knowledge continuously improve.
- Most experts agree that HIV DR testing should be a part of routine HIV care in Europe.
- DR testing should be an integrated part of a comprehensive HIV care programme.

Cons

- Drug resistance testing is costly.
- New drugs may be difficult to obtain.
- Testing may be difficult in early failure when there is low VL.
- Minority variants may be important.
- Testing mainly scores current therapy, there is poorer scoring of earlier therapies.

There are other challenges to surveillance of resistant HIV transmission, including:

- geographic and temporal comparability
- lag time between infection and diagnosis
- reversion of mutations following transmission
- lack of a recognized mutation list
- constant discovery of new mutations and drugs
- difficulty of maintaining updated mutation lists for re-analysis.

Discussion

As HIV DR testing is an integral part of a comprehensive treatment programme at a population level, WHO has spent extensive time setting up an HIV DR network to do surveillance of emerging resistance and transmission of acquired resistance in naïve patients. Additionally, WHO is pushing for early warning indicators that should go immediately back to the programme so that emerging drug resistance is recognized without delay. In northern Europe more than 90% of patients are fully suppressed, probably because there is an aggressive programmatic approach and team work. This needs to be evaluated and can also be used to set standards.

As DR testing constantly evolves new algorithms in pace with new drugs and technologies, it is important that a number of studies be undertaken to ensure accuracy. If differences are found in

study results, it is a sign that the evaluation of the drug is questionable or weak. If there is only one standard first-line and second-line regimen choice, then DR testing is not really needed, as the results will not influence second-line choice, and switching is essentially based on what is available for second-line therapy.

It would be helpful if WHO recommended classes of drugs with each regimen; then testing would be unnecessary. An algorithm could then be developed indicating if drug class A or B has failed and continue on to class C or D. This would be especially useful for first-time failure. Cost effectiveness and cost-benefits need to be considered when making recommendations. Middle income countries need to know costs so they can make rational decisions in allocating their resources. One of the problems of moving from the optimal to establishing a feasible standard is the total lack of information about cost-effectiveness.

General discussion

Minimal monitoring requirements

Everyone agrees that people not under treatment need to monitor CD4 count as it guides the physician on when to initiate therapy. As soon as patients are under treatment, VL measurements should be undertaken. This should be done fairly intensely to start and in the second, third or fourth year of treatment the interval can be increased. Consensus is that once the patient is started on therapy, the CD4 should continue to be monitored. It need not be monitored as frequently as VL, which needs to be reacted to more quickly in case of variations. Once the decision is made to start therapy, it is important to do both CD4 and VL baseline measurements that can be used in following the patient.

Frequent monitoring has advantages and disadvantages. A disadvantage would be the burden on the patient in terms of cost and time. Frequent monitoring in the first year of therapy can also be used to encourage the patient by showing that there is an improvement, that the VL is decreasing and the CD4 increasing. After the first year of treatment monitoring can be reduced to lessen the burden on the patient.

When to monitor

After a baseline VL, monitoring should be done in months 1, 3, 6 and 12 of the first year, thereafter twice a year; CD4 should follow the same monitoring intervals. If one monitoring should be taken out, the least important month is the first.

Resistance testing

DR testing may be of interest for determining patient resistance types in case a third-line regimen is needed at some point in the future. In addition, it is also needed in order to make a choice of second-line ARVs and to make sure that there is no resistance overlap. If WHO recommends TDF in first-line therapy, a DR test would not be needed to show that ZDV is effective in second-line.

It is optimal but not necessary to do a DR test. There are wide implications if a second-line regimen can be based on treatment history and not necessarily by resistance information. Resistance information would be helpful to make decisions regarding third-line regimens, but is

it necessary? To declare DR testing necessary when some countries are still struggling with VL testing may not be reasonable.

Information is needed on patterns of resistance across the population to recommend future therapy options, but not on the individual patient level, particularly if third-line or deep salvage options are available. However, DR testing in individual patients is useful since it can indicate if the virus has mutated. For example, among patients with a virological failure of first-line regimen with thymidine analogues, only 25% are expected to have a virus with thymidine analogue mutations. This information is clinically helpful, as physicians may consider using thymidine analogues on those patients without evidence of resistance.

Consensus and recommendations

Regional consensus was achieved on the goal of ART, the definitions of first- and second-line failure, when to switch and the minimum monitoring requirements of VL and CD4 for ART patients.

Goals of ART

- to maximize life expectancy (to that of normal life expectancy) and quality;
- to minimize risk of drug resistance and toxicity;
- to reduce the risk of HIV transmission.

Definition of first-line failure

Poor adherence issues and drug interactions need to be ruled out before failure is confirmed.

Virological failure

- primary virological failure – no response by patient, i.e., VL does not decrease to < 50 copies/ml on two different occasions after more than six months of ART;
- secondary virological failure – viral rebound, i.e., VL >50 copies/ml confirmed.

The virological failure scenarios are not necessarily indicators for a switch.

Immunological failure (CD4 cell count, if VL is unavailable)

- 25% drop from the patient's maximum level or
- failure to increase CD4 cell count > 50 cells/mm³ during the first year of ART.

Basing ART failure on solely clinical grounds is considered a suboptimal approach; countries are encouraged to ensure at least regular CD4 monitoring is in place.

Strategies for switching ART regimens

If the second-line regimen contains drugs that exclude the possibility of cross resistance of the first-line regimen the patient is currently failing, then a resistance test is not necessary in order to make the switch.

Early switch: VL > 400 (> 50– < 1000)³ copies/ml.

- Advantages: preservation of treatment options, higher likelihood of effective response, decreased risk of non-AIDS and AIDS related events.
- Disadvantages: high costs and more rapid exhaustion of ARV drug options; need for routine VL laboratory testing.

Late switch (VL ≥ 1000 – 10 000 copies/ml or a 25% drop in CD4 count)

- Advantage: reduced costs.
- Disadvantages: greater accumulation of resistance mutations and potential enhanced transmission of resistant virus; may compromise treatment response; may limit the choice of active ARVs for second-line therapy.

If at 6 months VL >50 copies/ml, the physician before switching to second-line treatment should assess and address adherence, drug toxicity (substitute toxic drugs) and any drug interactions.

The long-term implications of neither approach are known and studies comparing the switch management approaches are urgently needed.

Minimum monitoring requirements

- VL should be part of the standard of care of PLHIV
- VL should be undertaken prior to initiation of ART and then at months 1, 3, 6 and 12; subsequent monitoring may be at longer intervals for patients responding well to treatment.
- VL every 6–12 months is acceptable if there are local constraints on access or cost.
- CD4 cell counts should be done prior to starting ART, then two to four times in the first year; subsequent monitoring may be twice annually.

Definition of second-line failure

The definition is the same as first-line failure but the management differs depending on available drug options and greater use of drug resistance testing. New drug classes should be introduced where possible.

Drug resistance testing

If HIV DR testing is not available after first-line failure, a blood sample should be taken and kept frozen in the event that second-line failure occurs; both blood samples, after first and second-line failure, should then be tested in deciding on a salvage regimen.

³ More than 50 copies/ml, but less than 1000 copies/ml refers to the secondary definition of first-line failure, switching within this range of VL is an early switch.

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