Consultation on WHO ART Guidelines

'Voting with your feet on antiretroviral treatment'
IAS 2009, Cape Town, South Africa

Global Network of People Living with HIV
Treatment Action Campaign

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Executive Summary

This report presents the key points and recommendations that emerged during the 'Voting with your feet on antiretroviral treatment' meeting, a technical consultation on the upcoming revision of the WHO's Recommendations for Antiretroviral Therapy (ART) for HIV Infection in Adults and Adolescents (ART Guidelines), held 20 July, 2009 during the International AIDS Society Meeting in Cape Town. The consultation was co-organised by the Global Network of People Living with HIV (GNP+) and the Treatment Action Campaign and aimed to:

- To gather the perspectives and values of people living with HIV (PLHIV) and their families related to the upcoming revision to the ART Guidelines, namely:
    - How should issues of cost of treatment be weighed against issues of access in the HIV treatment services available in resource-limited settings?
    - What should the guidelines say about when antiretroviral therapy should be initiated?
    - In clinical situations where there is not enough evidence to be certain what the best treatment decision is, what treatment options do PLHIV want, and how would they make their treatment choices?
    - How do PLHIV feel about the potential use of ART for HIV prevention?

The theme 'Voting with your feet on antiretroviral treatment' was chosen to encourage meeting participants to consider whether there was a difference between what they would recommend (on the basis of evidence and cost) for HIV care and treatment programmes public health systems, versus what they would choose for themselves or their family in a particular situation (what option would they walk or run to for themselves?).

This perspective is often missing from guidelines developed by technical experts, programme managers, clinicians and researchers. So WHO approached GNP+ and other organisations representing and advocating for PLHIV and offered them the unprecedented opportunity to provide input on the guidelines revision that will shape the kind care available for PLHIV for years to come.

The meeting was attended by about 30 PLHIV, about a third of whom were from South Africa, a third from the rest of Africa, and a third from Europe, the US and Asia. Participants had a quite a broad range of treatment experience — from those who were not yet on ART, to some who were on their first-line regimen and some who were much more heavily treatment experienced.

Consultation participants agreed that many of their lives could be directly impacted by the revised Guidelines. However, they also noted that in many of their countries actual clinical practice was rarely up to the standards recommended by the ART Guidelines — including the treatment they themselves had received.

This was one reason why participants stressed that WHO needs to take great care in the language included in the revised WHO guidelines. The minimum standard that WHO suggests is acceptable for HIV programmes will be the most that many governments will conclude that they need to provide. For instance, there was widespread agreement that the guidelines should recommend that treatment be initiated once CD4 cell counts fall below 350, and several people present said that the old standard, starting treatment only after CD4 cell counts fall below 200, should not even be mentioned in the revised guidance.

Likewise, while many attending the meeting acknowledged that their health systems are facing real financial, infrastructure, and human resource constraints, there was broad consensus that WHO should be cautious about including considerations of cost in the revised guidance, lest it inadvertently establish a lower quality of care for poorer countries. PLHIV everywhere should have access to the best ART regimens and appropriate laboratory monitoring. These choices should be made on the basis of clinical evidence rather than cost.

For instance, tenofovir should be recommended as part of first line regimen (which could lead to it being made more affordable) — while the use of d4T should be discouraged on account of its toxicity. Likewise,

viral load monitoring should be made available and affordable to confirm the need to switch to second line therapy.

That being said, there was general agreement that the other expensive treatment options, that are standard of care in industrialised countries (such as frequent laboratory monitoring), are not necessarily better or suitable for every setting. In fact, in some situations, the participants voiced a clear preference for the simpler options being employed by the public health approach to HIV treatment. For instance, for people who are clinically stable, it was suggested that fewer clinic visits and less intensive laboratory monitoring would actually be more patient-centred.

For the many difficult clinical situations where there is inadequate evidence about which treatment options are best, participants discussed how they approached such treatment decisions in general. For instance, many expressed concerns about the toxicity of treatment, treatment readiness, and stated a preference for a less medicalised and more holistic approach to treatment and care — until clinical data clearly demonstrates that more aggressive and/or complex care treatment approaches are truly in their best interest.

Finally, there was also general agreement that the purpose of ART first and foremost is for health and well-being of PLHIV, although, in some situations — such as the prevention of vertical transmission to infants — it clearly can be used for prevention. Of note, several people present said that they hate the term “mother to child transmission’ because it demonises the mother, and would prefer a shift to the term ‘vertical transmission.’

While there was interest in the further clinical study of the potential of ART for prevention, there were also concerns about whether going on treatment earlier (for the sake of prevention) would truly be in the best interest of PLHIV, or the best choice for their own health. Furthermore, some were concerned that if the approach were not as effective as its proponents are suggesting, that could result in more HIV transmission and possibly transmission of resistant virus, particularly in resource limited settings where there is not routine access to viral load.

"The WHO ART Guidelines have direct impact on the lives of people with HIV and on the care we will be receiving in our countries… The guidelines are critically important to us because our countries use it as a gold standard. They treat whatever WHO puts into the guidelines like it is engraved in stone."

Vuyiseka Dubula, South Africa's Treatment Action Campaign (TAC).

First published in 2004, the ART Guidelines are crucial reference tool for countries with limited resources that have been attempting to scale up HIV care and treatment programmes including the provision of ART. The guidelines adopted a 'public health approach' to ART management with an emphasis on improving survival at the population level in contrast to the highly individualised approach common in industrialised countries. This involved consolidating available treatment options into two sequential regimens (first- and second-line ART) with streamlined approaches to clinical and immunological monitoring. This simplified approach greatly facilitated the introduction of ART in many countries, and almost all the high burden countries soon used the ART Guidelines to frame their national policies.

Since first being drafted, considerable more clinical data and programmatic experience on the use of ART in resource limited settings have become available. In 2006, the guidelines were revised to take into account the availability of more drugs, the use of ART in women (and pregnancy), and concurrent treatment of HIV and tuberculosis (TB) and hepatitis B and C.

But the field continues to evolve (see box).

In the current revision, it should be possible to refine the ART Guidelines to improve the standard of care being offered PLHIV — but the choices are not always clear-cut — particularly in resource limited settings.

"The next revision of the guidelines," Dr Marco Vitoria of WHO told participants at the GNP+/TAC meeting, "will still be evidence based —what science is saying — but we are now trying to consider other domains that can help us to make a recommendation that can be useful to maximize the benefit and minimize the risk for people living with HIV worldwide

Much of the success of the ART Guidelines can be directly tied to the profound efficacy of the simple first-line regimens anchored by non-nucleoside reverse transcriptase inhibitors (NNRTIs: efavirenz or nevirapine) in combination with a nucleoside analogue 'backbone' such as AZT/3TC (Combivir) or d4T/3TC, or in some situations, a triple nucleoside analogue combination anchored by abacavir or tenofovir, such as in pregnant women on TB therapy (more on this below). But over time, the toxicity of some of the agents involved in the ART regimens, in particular, d4T, have become problematic, with people more likely to change their treatment regimens because of drug side effects than due to the loss of antiretroviral activity associated with the development of drug resistance.

Furthermore, because of the durable efficacy of first line ART, the approach to managing treatment failure and switching to second line therapy in the ART Guidelines has remained relatively untested in the field. But now that many PLHIV have spent several years on their first line regimen, this is no longer the case; and there are major differences of opinions among researchers and other key experts over how best to make the decision to switch to 2nd line treatment.

More evidence has also become available suggesting that starting ART earlier in the course of disease (when CD4 cell counts are higher) can achieve better health and survival. The current version of the ART guidelines recommend that ART should be 'considered' when CD4 cell counts fall below 350, but they also state 'the optimal time to initiate treatment between 200-350 cells/mm3 is unknown." (It should be noted however, that some countries still have only limited access to CD4 tests, so the guidelines also stress that ART can be initiated on the basis of clinical staging for PLHIV with signs or symptoms of advanced disease.)

Since that time, the SMART study reported that untreated patients with a CD4 cell count below 350 cells/mm3 had an increased risk of not only HIV-related illness, but some other serious conditions, including heart, kidney and liver disease, as well as some cancers. In response to this data, industrialised countries revised national recommendations to start ART when CD4 cell counts are in the region of 350. Since then, several large studies, including two very large cohort studies (with close to 40,000 participants) in mostly industrialised countries have both released consistent results: there is a significantly greater risk of AIDS or death when PLHIV wait to start ART after their CD4 count falls below 350. However, the studies show contradictory evidence on what CD4 cell threshold above 350 cells is best to use for starting treatment.

Of course, results from studies in the developed world cannot be extrapolated to resource-limited settings. However, recent evidence from Haiti has clearly demonstrated a 4-fold reduction in mortality (and TB cases) in people who started ART when their CD4 cells were between 200-350 versus when they start treatment after their CD4 cells fall below 200.

considering contexts that exist in different parts of the world."

Considerations of what should be included in the revised ART Guidelines, and the weight given to recommendations

- A review of the evidence, with a focus on what are the most critical outcomes for PLHIV
- An assessment of the risks and benefits of selected interventions (action, or drug recommended)
- Assessments of the cost and feasibility of implementing an intervention into different resource limited settings (the greater the cost-effectiveness, the stronger the recommendation)
- An assessment of the **acceptability** of the intervention to
    - programmers/policy makers
    - health care providers, and
    - ***PLHIV***

The meeting in Cape Town represented the start of a unique consultative process between WHO and communities of PLHIV, to understand what PLHIV want from their treatment programmes, and what will and will not be acceptable to include in the next ART guidelines revision. PLHIV were asked to consider how they would 'vote with their feet' regarding these treatment choices: For instance, would their recommendations for the guidelines (that will frame the options available within the public health system) be different from the choices they would make for themselves and their own health if they could afford different options outside the public health system?

"I think this is the most important meeting in this conference because I have the opportunity to see a different perspective that's been missing in the WHO guidelines and that we are now trying to incorporate in the new version we are starting to prepare," said Dr Vitoria.

Major issues that could affected in the 2009 revision

- When to start ART?
- What to start with? (Safety considerations may change if some antiretroviral agents are used earlier, for instance, it is not clear how safe nevirapine is in women with CD4 cell counts over 250)
- How should programmes monitor for treatment failure and when should people be switched to 2nd line regimens?
- What should be used for 2nd and 3rd line ART?
- How should ART be used in PLHIV who have other conditions at the same time (such as pregnancy, TB, and hepatitis B or C?)

Finally, there has been a surge of interest in the use of ART as a prevention tool — to prevent the onward spread of HIV to discordant partners and at the population level. At least one mathematical model suggests that widespread HIV testing and immediate treatment of PLHIV could actually stop the spread of the HIV epidemic. So another goal of these technical consultations is to assess how PLHIV feel about this new consideration in the "when to start treatment" debate.

The discussion groups and background on their questions

In light of these questions and the major considerations being in the revised guidelines, meeting participants were divided into 3 groups that addressed these issues though each through a somewhat different lens.

Group 1 was asked to address the following questions, considering how to balance quality of care (which is sometimes more expensive or complicated to deliver) with equitable access to care.

- What should be the CD4 threshold the guidelines recommend for when ART should begin, in light of the fact that earlier treatment will increase the demand for ART in programmes that are already facing severe constraints?

  Essentially, should the guidelines explicitly state that treatment should begin when CD4 cell counts fall around 350?

  If there are limits to how many people a programme can afford or has the capacity to put on treatment, then offering earlier treatment could lead to a situation where programmes reach the limit of their capacity and can no longer put new people on treatment, or mismanage drug supplies. If this happens, there are concerns that when some sicker and more vulnerable people present for care, they may not be able to access ART, or programmes may have stock outs — and lead to treatment interruptions for people with more advanced disease.

- What do people believe is the appropriate clinical and laboratory monitoring for people living with HIV in order to preserve treatment options and avoid poor outcomes?

  A variety of laboratory tests are routinely used in industrialised settings to assess the safety for starting treatment, the time to start treatment, the effectiveness of treatment, and to monitor for treatment failure.

  The ART Guidelines are quite clear that settings without access to laboratory tests can still initiate people on treatment on the basis of clinical staging (signs and symptoms of advanced HIV disease). However, WHO also supports wider access to CD4 cell tests in order to determine when to start treatment (when CD4 cells fall below a certain threshold, such as 200 or 350 CD4 cells).

  However, numerous studies are demonstrating that neither clinical monitoring or CD4 cell count tests are very good indicators of whether an ART regimen is still exerting an effect on the levels of HIV in a person's body. Only viral load tests, widely available in industrialised countries, can do that. However, the infrastructure to perform viral load tests has yet to be scaled up in many countries, and is quite expensive. There are also questions about what level of viral load suggests the need to switch treatment (detectable virus, or viral loads above a certain threshold, such as 10,000 copies/mL)?

  Routine viral load testing would be extremely expensive, and there are questions about whether it is really necessary. Other researchers are looking at the use of targeted viral load in order to confirm immunological or clinical indications of treatment failure — and have shown that it may be more costly to switch to expensive second line prematurely on the basis of immunological or clinical failure.

  One criticism of this approach, however, is that for the money it will take to scale-up viral load, many other people could be initiated on first-line treatment.

- What are the strengths and weaknesses of tenofovir versus d4T versus AZT as part of the nucleoside analog backbone in the first-line regimen?

  d4T was included in WHO recommended first line regimens on account of being initially better

tolerated than AZT, because it could be given without requiring haematological screening (which was felt to be necessary for AZT) and because it was available in the cheapest fixed dose ART combinations. However, after several months, there have been extremely high rates of regimen limiting treatment toxicity including life-threatening lactic acidosis, peripheral neuropathy, lipoatrophy and fat redistribution (including breast enlargement in men).

AZT has been widely used and is preferred in pregnant women. However, it is harder for people to tolerate at the start of treatment (initially causing nausea and vomiting), and it can cause serious anaemia. However, long-term metabolic toxicity is somewhat less common than on d4T.

Tenofovir is the newest agent, which has quickly become the preferred choice in industrialised countries. However, at present, it is considerably more expensive than d4T or AZT. Initial side effects are mild. Some would say is less well characterized than the two older drugs, and there are questions whether it could have longer-term toxicities (to the bone and kidney). So far, these have been reported to be rare. There have also been concerns about the safety of using it in the absence of kidney function tests — though the findings of the DART study released at IAS2009, suggest that such tests may not be necessary to administer tenofovir safely in Africa. Finally, there has been less data on the safety of tenofovir in pregnancy or young children (there is some concern about it having an effect on bone development in the foetus). Thus far, however, birth registries suggest no increase in congenital abnormalities in infants born to mothers taking tenofovir.

Group 2 was asked to discuss the following questions pertaining to the use of ART for HIV prevention, through the lens of Positive Health, Dignity and Prevention — considering prevention together with the needs of PLHIV for treatment, care, support and human rights.

- Does taking ART have a role as a HIV prevention method, and if so, what is it?

- Should all women living with HIV who are pregnant or trying to get pregnant start ART instead of just taking short courses of ARVs for the prevention of vertical transmission?

  In industrialised countries, the standard practice for most HIV positive women who become pregnant is to go onto ART, regardless of their CD4 cell count, in order to provide more complete protection against vertical transmission to their infants.

  In resource-limited settings, different countries have somewhat different CD4 cell count thresholds for when pregnant women should begin ART. Above this threshold, women are given a short course antiretroviral drugs (the exact regimen varies, but it is usually AZT in the third trimester, and a single dose of nevirapine (sd-NVP) during labour, along with sd-NVP for the infant).

  However, some experts are now recommending that pregnant women in countries with limited resources should be given ART at a higher CD4 cell threshold than for other PLHIV.

- How willing would people be to take part in trials of taking ART perhaps earlier than now thought to be necessary for their own health, particularly in order to see if it prevents HIV being passed on to others?

  Early ART may well have other benefits besides the potential use for prevention, however, the primary endpoint of some of these studies could be prevention.

Group 3 was asked to consider clinical issues where the evidence base is hard to interpret. What would their preferences be in these situations, and upon what evidence or principles would they be basing their choices?

- How early is too early and how late is too late to start ART?

The clinical data suggest that waiting till CD4 cells fall below 350 may be too late to start treatment, however they are unclear about when is best to start. When do PLHIV in resource limited settings want to start treatment and why?

- If your CD4 cell count does not increase on treatment (or falls a little) should you be switched to second-line therapy? What if you have an undetectable viral load?

  What would PLHIV who aren't doing very well on treatment want to do, knowing that there may not be any remaining treatment options for them after switching to second-line ART? Would they want a viral load measurement first? How would they feel about that if their last CD4 cell count went from 650 to 600? How would they feel if their last CD4 cell count went from 210 to 180?

- ART should be started in people living with HIV who have active TB while they are on TB treatment. How do we do this in practice knowing that ARV medicines and rifampicin may interact?

  There is now mounting clinical evidence demonstrating that PLHIV with active TB disease who begin ART while they are still on TB treatment are much more likely to survive. However, the precise time to start ART (simultaneously, after one or two months on TB treatment) is still unclear.

  The decision is also complicated by drug interactions between rifampicin and many of the ARVs. For instance, rifampicin lowers levels of nevirapine and the protease inhibitors. Efavirenz is the preferred option, but may not be safe in pregnant women with TB. A triple nucleoside analogue combination may be an alternative, but there are questions about its potency relative to NNRTI-based regimens and how it might affect subsequent ART options?

Reports back, discussion and feedback

Given the rather short time that the groups had to report back to the meeting, the following has been augmented with comments recorded during the group discussions. Also, some participants made comments pertaining to another group's questions — these are included where relevant.

However, it should be noted that the matter of cost of care came up in all the discussions. While recognising that public health systems are operating under real infrastructure and human resource constraints, many PLHIV at the meeting expressed strong reservations about whether the financial cost of an intervention should really be factored into the ART Guidelines:

"We keep on talking about poorer countries and cost implications but I would really say 'Universal Access' means universal standards. You must have the same standards everywhere. Otherwise it's not acceptable," said one woman from Nigeria

"I'm not comfortable with the price coming into the guidelines at all. We don't need to talk about the guidelines and affordability. It's not our job to talk about. Aren't guidelines supposed to be based on clinical evidence?" said a participant from India

"You will always find, sitting in a room of PLHIV activists, that when somebody says it's too expensive, you say "WHY? We don't believe you" and number two, "take things to scale!" When countries take things to scale, it reduces the price," said another activist.

Group 1

Question 1: Should the guidelines recommend earlier treatment (when CD4 are around 350)?

"The WHO ART Guidelines should specify that ART should be available at 350 CD4," the group's rapporteur said, "though the guidelines should also recognize the range of error in CD4 testing and state that a slightly higher CD4 cell count shouldn't be grounds for refusing treatment."

Participants were quite passionate about these points.

"We need to be really explicit about this because people are looking for any excuse not to let this change in the WHO guidelines," said one participant.

"We don't want to see anywhere in the WHO guidelines, anything that says to 'start at 200.' Because if we still put 200, some governments are still going to be using 200 as a criteria," said another.

Participants suggested that governments interpret the ART Guidelines quite rigidly in order to provide as little care as possible.

"If for example, the guidelines continue to say start treating when CD4 cell counts fall below 200, governments will use it as an excuse to continue to turn away people seeking treatment whose CD4 cell counts is 210 — and they often don't make it back before they have developed a serious AIDS-related illness," she said.

Such a case was mentioned in the group discussion. Because monitoring is performed at regular intervals, sometimes a person will come in with symptoms before they are due for another CD4 cell test, but when their last CD4 cell count was above 200, their symptoms may be disregarded.

"Sometimes this even happens when a person is showing symptoms. Sometimes, even if they have an AIDS defining illness, they are not given treatment," said one group member. "There is a girl who passed away about 3 weeks ago —she had CMV. But nobody was 'able' to check her out. She was given a referral letter from the clinic to the hospital. At the hospital, they did not check her eyes, they just said: 'no, just go and eat more carrots and then go and see an optometrist!' Then she went back to the hospital, because she could not see. Two days later she was admitted into a hospice and a week later she died."

According to current WHO guidelines, of course, those symptoms should have been investigated and would have been cause for starting ART — even without another CD4 cell count. But where CD4 cell counts are available, programmes look at the numbers — which need to be higher to prevent events like that from ever occurring.

As to whether participants were afraid that recommending earlier treatment would lead to programmes running out of ARVs or not having enough drug for when more vulnerable people (with lower CD4 cell counts) present for treatment, it was noted that "even at the 200 level, a whole lot of people are not being treated."

"The most vulnerable people are still not on treatment - even with the guidelines at 200! So we are not changing anything, really, by asking for better drugs and for earlier clinical treatment. We'll do the same thing we've always done - fight for better drug prices and fight for better services," said one group member.

"I don't want to be reasonable and say that 200 is okay. No, I think we have to fight for 350 despite the fact that it will increase the burden of services. But we will have to deal with that thereafter and we will have to deal also with human resources issue," said a participant during a different group discussion.

Question 2: What is the appropriate level of laboratory and clinical monitoring?

Most of the discussion focused on the need to have some access to viral load.

"Viral load should become an important part of monitoring for PLHIV on treatment, especially when considering changing meds," the group's rapporteur said.

Group members felt that a strong statement was needed stressing the importance of viral load testing to, at the very least, confirm treatment failure.

"In this version of the book it starts off, 'Although viral load testing is not yet widely available...' Now we know that is true but it sort of lets people off the hook from not trying to make viral load monitoring available," said one group member.

There were a range of views about how routine viral load monitoring would need to be, however.

"There's a difference between having a viral load every three months or every six months, or using a strategic viral load just to confirm whether the change or lack of change in CD4 cell count has anything to do with whether somebody has become resistant to therapy," said one meeting participant. "We need to at least be able to put in enough capacity in programmes to confirm failures before switching treatment."

As for concerns that the money used to scale up access to do routine viral load might be better used putting more people (perhaps thousands) on first-line treatment?

"What we were saying is there needs to be a level of viral load monitoring. We are not saying that with each and every appointment when you come, we'll do a viral load. At some point after going on ART, maybe one viral load per year when you are stable- at least I won't feel ashamed that I have denied 20 000 people treatment — I might have denied 10 people. But this is important for me too," said one group member.

[At the end? An important principle seems to be emerging out of these discussions: that the rights of those who are not yet on treatment do not supercede the rights of those who are… Otherwise, the same argument could be used to deny people access to second-line ART because it is many times more expensive than first-line. Doing what is necessary to maintain the health of a PLHIV who has already made the effort to go onto treatment is important as well.]

"I have a feeling that even from an economical point of view, it will cost less to investigate further — even with viral load, and even, if it's available, with resistance testing — than switching too soon to second-line therapy," said a participant in another group.

There was also a brief discussion on the appropriate amount of clinical and laboratory monitoring in general — in the work-up before going on ART, and when people are relatively stable.

"I take treatment at a public sector clinic, and we have established things called 'A stable patients' adherence club,'" said one group member. "We only come to the clinic six times a year, we only see a doctor once a year because there are very few doctors. In the meantime, we are only seen by a nurse when it's needed. Most of the time we see each other, help each other, we get meds from the pharmacy and it reduces the burden that I have to take time away from work. I'm only needed there when I need to do blood monitoring twice a year. I don't have to come in the other times, I can send somebody else to go and fetch my medication. Because the clinics are saturated seeing people who are already on treatment — we are taking up space for those who need to be initiated on treatment. We are doing a review of the clubs right now but already we are starting to see signs of people with the numbers of new initiations are increasing"

Several others said that although they want monitoring to be available when needed for important treatment decisions (again, especially to determine the need to switch treatment), they would otherwise welcome less frequent monitoring when they are stable on treatment.

“Requiring too many clinic visits can really just be a way of putting people off from actually accessing what they have as a right for health!” said another meeting participant.

Question 3: d4T vs AZT vs tenofovir:

“All of these drugs have their disadvantages and advantages,” said one member. However, there was broad consensus upon a number of matters.

1) Tenofovir *must* be made available as part of first-line ART — and the price must be reduced so that it becomes affordable for public health systems. Many felt that if tenofovir were made part of first line regimens, there would be increased pressure to increase generic production and lower its price.

“Tenofovir is more expensive than d4T, we know,” said one group member. “As we initially fought for d4T to be less expensive, we will fight for tenofovir to become less expensive. By not making demands, we could be perpetuating the situation, by making tenofovir first-line, it should or could lead to price reduction.”

Group members did say they wanted to see more long-term safety data on tenofovir’s use in sizable African cohorts. Incidentally, such data were presented the very next morning at IAS from the DART study, conducted in Uganda and Zimbabwe. Most of the participants in the study were on a tenofovir-based triple nucleoside analogue regimen, and after nearly 5 years of efficacy and safety data, survival was quite good, at around 90% (and 87% among those managed clinically, without any laboratory monitoring).

2) Continuing to recommend d4T as part of the preferred first-line regimens *is not* acceptable:

“In our context in South Africa, d4T is definitely *not* an option for women — it may not really be an option for anyone at all,” said one group member during the discussion. “Toxicity is present in increasing numbers of women - both lipodystrophy and lactic acidosis - amongst women who started on d4T.”

“Definitely d4T is out - for us it has been totally thrown out of the guidelines. Even those who are on d4T are being switched, except for those who say “I want to remain on it!” said one woman from Nigeria.

One woman in South Africa even ‘voted with her feet’ against d4T, going to great lengths when she started treatment to be prescribed the only available alternative in her country at the time, AZT. She remains on AZT even though she has anaemia that is so bad that she “feels cold all the time. In winter in Cape Town, I have to wear three suits because I can’t feel my feet, they are freezing cold, and my hands.”

Even so, she is much more against d4T.

“My sister had to start treatment and I said: ‘I refuse, you are NOT going to be taking d4T! I would rather you change all clinics in South Africa and go all over from one clinic to the next!’ so we ran around to all the clinics, until one agreed not to use d4T.”

AZT is clearly an alternative, although the risk of anaemia is a serious concern in many African countries where it is an endemic problem.

One remaining concern about tenofovir was its safety during pregnancy.

“In my case I was on tenofovir when I became pregnant and I had to change because my doctor was not sure

about the safety of tenofovir in pregnancy," said one participant. Group members were uncertain whether these concerns have been adequately addressed yet.

In general, there was a lot of discussion about how any of these drugs affect pregnant women and the need for a better review of the evidence that should be reflected in the guidelines, since there are many pregnant women on ARVs in resource poor settings (further comments about pregnancy and ART have been incorporated into Group 2, question 2).

Finally, participants said that the idea that only one or two regimens would be available in resource-limited settings *is not acceptable* and the ART Guidelines need to reflect this. "WHO needs to make universal guidelines for first, second, third *and fourth-line treatment* so that people have an idea of what they should be able to expect," said the group rapporteur. Since the drugs used in ART could affect subsequent treatment options, class-wide drug resistance issues need to be considered in the selection of these regimens.

Group2

Question 1: Does taking ART have a role as an HIV prevention method? And if so, what is it?

There was consensus that ART is first and foremost a way to improve the health and well being of PLHIV, although, in some situations, such as the prevention of vertical transmission to infants, it clearly can be used for prevention.

Prevention could perhaps be seen as a consequence or added benefit of ART but should not be its primary goal. In fact, many in the group were uncomfortable with ART being seen as an alternative prevention method (although it may confer additive protection).

There was discussion about the Swiss Statement that concluded after an extensive review of the literature that a treatment adherent PLHIV who has had an undetectable viral load for more than six months and with no co-factors such as the presence of sexually transmitted infections (STI) would have a very low or no risk of onward transmission.

Some participants in the group felt more evidence was needed in resource limited contexts. One woman noted that, at present, she would not be confident of her partner being protected, even though she has been on treatment for 9 years.

"I'm HIV-positive and my husband is negative. I wouldn't risk putting him into a position of getting HIV by just saying that I'm on ART or he might be infected" she said.

Clearly reducing viral load would lower the risk of transmission, and ART on a mass scale may reduce the burden of HIV at the population level in the absence of complete behavioural change. However, there is a danger that this approach might lead to the treatment of PLHIV against their will or before they are ready.

There were also concerns that if ART were seen as a prevention method it might discourage people from having safer sex. Others said that this is an assumption that will need to be studied further to see if it is true — people may continue to use condons because there are other sexually transmitted diseases that people do not want to get. At the same time, however, the desire to have unprotected intercourse (and enjoy full sexual and reproductive rights) is quite strong. For instance, many serodiscordant couples take this risk in order to have children.

If this were to occur in a context without routine access to viral load (to confirm that someone has an undetectable viral load in the first place), people who believe that ART is a prevention strategy may continue to have unprotected sex long after their treatment has failed. This might not only spread HIV, it might spread drug resistant strains. Thus the strategy, if it works, may only be safe with increased access to viral load.

A participant in another group discussion suggested that, in contexts where the 'ART as prevention' approach is being considered, access to viral load may become a new human right — that PLHIV will have a right to know whether they are infectious or not. However, it was also pointed out that checking one's viral load isn't like checking blood sugar levels. There are, as of yet, no cheap point of care viral load tests that can tell a person their viral load at the moment. Furthermore, people often do not know whether they have contracted an STI and even common conditions such as urethritis or bacterial vaginosis may increase genital viral load.

During feedback discussion, it was noted that the complete burden for prevention should not be placed upon the HIV-positive partner. Another approach to keep a serodiscordant partner HIV negative would be for them to take antiretrovirals as pre-exposure prophylaxis (PREP). There was consensus that further study of this approach is warranted, and that, if it works, it could help grant PLHIV full sexual and reproductive health rights while providing a tool to protect his or her partner.

Finally, the group also noted that ART does 'prevent' opportunistic infections from developing. While the

core question was about HIV prevention, this observation could have important consequences when it comes to other communicable infection, such as TB. At IAS, new studies from the Western Cape of South Africa reported that there has been a stabilisation in the rates of TB across the population in periurban communities where most PLHIV with advanced disease have now been put on ART. This raises a sticky issue if PLHIV who are not on ART start being blamed for TB in the community, or if there is pressure for PLHIV to go onto treatment because it is 'good for the health of the community.'

Question 2: Should all women living with HIV who are pregnant, or trying to get pregnant, go onto ART or just take short course ARVs to prevent infection of their baby?

There was broad consensus that it is important to treat both the mother with HIV and her child —not one or the other, but both.

However, there were a range of opinions about the best approach to treatment and prevention in this population. While everyone was in favour of access to a short course of ARVs to prevent the transmission of HIV to the infant, many in the group — some being mothers themselves — did not believe that full ART was necessary for all potential mothers with HIV or to protect their infants.

"Let's say I'm pregnant and my CD4 cell count is 1200. At that CD4 cell count, I don't need to yet be started on ART," said one woman.

Indeed, data suggest that women with high CD4 cell counts and low viral loads are much less likely to transmit HIV. In such cases, short courses of ARVs offered by programmes to prevent mother to child transmission (PMTCT) prevent most cases of HIV transmission to the infant.

On the other hand, most women with HIV who wish to become pregnant don't have such high CD4 cell counts. Rather, they may have CD4 cell counts that are just above the threshold for starting treatment in their local programme. Some meeting participants said women must have the right to go onto ART for themselves and their child — especially if the local threshold is at 200 CD4 cells. Clinical data now suggest that maternal and infant survival is better and HIV transmission is lower if women with HIV go onto ART, even with CD4 cells between 200 and 500.

A woman in another discussion group reported that she had gone onto ART simply because she was planning to become pregnant — and she wanted the best possible chance of protecting her health, her infant, and her partner.

"Right now we are in an era where ART is the best possible way to prevent the mother from dying but also the child from getting infected, and also, from preventing the father from getting infected if he is not infected," she said.

Some noted that PMTCT programmes have major problems with loss-to-follow-up after delivery, and attributed this to the fact that PMTCT programmes do not focus enough on the health of the mother.

"The messages that are being preached at the clinics are: 'You must save your baby, you must save your baby!' There is little emphasis on the well being of the mother," said one woman from South Africa.

However, others noted that during pregnancy, a mother is already vulnerable — and it may not be the best time for her to be making a lifelong commitment to taking ART. Some women may not really be ready to go onto ART right away — especially if they have only just learned that they are positive.

Another question is whether going onto ART versus PMTCT will affect future treatment options? Although data suggest that ART remains effective in women who have been in PMTCT programmes (if begun about a

year after pregnancy), many women with HIV are having multiple pregnancies, and there is little data to show how multiple exposures to ARVs in PMTCT will impact on subsequent response to ART. At the same time, however, if women with higher CD4 cell counts begin taking ART before they are ready, adherence may suffer, and that could lead to treatment failure and fewer treatment options in the future.

Clearly, this is a choice each woman should make for herself without feeling pressured.

Part of the problem may in fact be the very term 'prevention of mother to child transmission' demonises women. Another important consensus that emerged was that people want the term dropped from the revised ART Guidelines.

"Mother-to-child-transmission suggests that the mother is the bad person," said one.

"Personally I hate the name 'Mother to Child', I hate that name because it means you as the mother have the burden of disease. It means, if for any reason, treatment fails and that child is born HIV-positive, then it is your fault. So that name totally turns me off," said another woman

"Let's re-brand it as vertical transmission," said many others.

Question 3: Would people be willing to take part in trials taking ART for prevention?

As indicated in question 1, many participants feel that ART for prevention could offer important additional benefit from treatment to PLHIV — but the concept requires further study, particularly in resource limited settings.

Many said that they might be willing to take in such a study.

"I've been on trials in the past and I went on trials simply because I knew that there's possibly a benefit for me but I also thought it was a way of making a contribution," one woman said.

"Many times there are white people from America or from Geneva that come to do trials," said one woman from Kenya. "But to me it's okay, anyway, if at the end of it all if that drug that they are doing the trial may work."

However, there was also consensus about considerations around ethics and informed consent for such a study:

- One would be whether the study is solely to determine the prevention activity of ART or to assess the benefits of earlier treatment? It would be important to look at the potential health benefits of early ART.

- The potential downsides of going into the study should also be explained to potential participants, including the possibility of experiencing side effects from treatment before HIV causes noticeable symptoms, the possibility of running out of treatment options before they are needed for one's own health.

- There needs to be support and services for people who experience side effects or illness in the study.

- How might participation in the study affect pregnancy?

- Participants need to be told about the outcomes of the study. Some noted that this often doesn't happen.

- Also, participation *must* be totally voluntary and up to the individual. Cluster-based studies, where village elders or community leaders give consent for their entire community to be randomised to one treatment approach or another, may not be appropriate for this type of study. Every PLHIV in the study setting needs to be given the choice for whether they participate in this sort of a study or not.

Group 3

It became apparent during Group 3's discussion on treatment decisions in situations where the clinical evidence is unclear, that PLHIV need more data to make informed decisions. So the group primarily focused on what was important to PLHIV, their fears and desires in relation to what they want from health services and the ART Guidelines.

Question 1: 'How early is too early and how late is too late?'

Group 3 acknowledged that PLHIV everywhere should have the right to go onto treatment when CD4 cell counts are in the range of 350 cells — in light of recent data showing that treatment at this point improves survival and decreased progression to AIDS and TB. While treatment is still beneficial even when started later, waiting until CD4 cell counts fall below 200 represents an unacceptable risk.

"Too late is of course a CD4 count of below 200 or after the first opportunistic infection occurred, and too early is when one is not prepared to start. It is not a clinical criterion. But there is a very strong link between the preparedness of an individual and his or her capacity to be 100 percent adherent," said one participant.

Some felt that treatment at higher CD4 cell counts, long before people with HIV experience symptoms, might be too early, because it would be before the person being treated could observe clinical benefits from treatment. Consequently, they may be less likely to be adherent to treatment if they experience drug side effects.

In the absence of data of showing that earlier treatment is better, there were very real concerns about the toxicity of ART, and whether initiating treatment too soon could limit future treatment options.

Indeed, it is a mistake to think that all PLHIV want to go onto treatment whatever the ART Guidelines recommend. Even people with CD4 cell counts below 200 and symptoms may be afraid to go onto treatment.

"Many ask, how could I take drugs for the rest of my life?" said one PLHIV from Uganda. "And when you are being prepared that these drugs has some side-effects i.e. vomiting, skin rashes, night mares and so forth, it creates fear. In addition, many of us come from countries without resources and are very poor — many are afraid to go onto treatment when they don't have enough to eat."

"People do not want to start treatment because of the side effects that they have heard of, or because they know other people who have died from side effects," said one activist from South Africa. She said that simple, straight-forward information, based on sound clinical evidence was needed to address these fears. Therefore, clearer evidence of the benefits of earlier treatment from resource limited settings would be needed to convince people at higher CD4 cell counts to go onto treatment.

Ultimately, regardless of what CD4 threshold the ART Guidelines recommends, the decision to go onto treatment is a personal choice, depending upon whether one feels ready for treatment or not. Unless PLHIV also have a life-threatening opportunistic infection, they should not be pressured to start ART before they are psychologically prepared for it.

Question 2: Should people who fail treatment immunologically (with a poor CD4 response) be switched to second-line therapy?

The ART Guidelines need to recommend further investigations to determine why someone's CD4 is failing, said Group 3's rapporteur who noted that he himself had been in this situation.

Investigations should include an adherence assessment — to make certain that an individual is taking their regimen correctly and consistently (and hasn't, for instance, taken a drug holiday). In general, participants felt

it important to have adherence projects in place and regularly assessing people on ART long before treatment failure sets in.

But if the person has been adherent and treatment failure is suspected, participants felt that it was absolutely crucial to be able to check viral load, to determine whether treatment is still working or not.

“There is no need to switch, if after further investigation, your viral load is very very low or undetectable,” said one group member.

Without access to viral load, there is a danger of switching unnecessarily to a more expensive and complicated second line regimen — and potentially using up all of one’s treatment options too soon.

Many people do have suppressed viral loads and are still failing immunologically, so discussion centred on what could be done in these cases.

One meeting participant stressed that this was linked to beginning treatment late: “The later you start, the less the chance that you – or your immune system – recovers,” she said.

However, it is also possible that the toxicity of some of the ARVs in the regimen are having a dampening effect on the CD4 response, and that a switch of regimens might be of benefit — even in people with suppressed viral loads. This option would be less risky if more treatment options were available in resource limited settings, complained one activist from South Africa.

But South Africa only has two regimens available. Why has South Africa got only two regimens? Why have some other countries got four, five regimens?” she said.

In the absence of other solutions, participants recommended ‘positive living.’

“After going on ART, the paradigm shifts. You have already taken your drugs and you are okay and you go back to drinking, smoking and having unprotected sex — and that can account for reduction in CD4 cell count,” said the group’s rapporteur.

Finally, immunological failure could indicate another infection as well, so further investigations should include screening for TB and other infections that could lower CD4 cell counts.

Question 3: How to start ART at the same time in people on TB treatment?

The ART Guidelines should stress the importance of integrating TB/HIV services, because of data demonstrating that people with TB who are coinfected with HIV don’t get on ART while they are still on TB treatment, have a much higher risk of mortality.

There was a range of opinion as to whether all TB patients should qualify for ART however. Some participants said that, unless CD4 cell counts were very low, the practice in their country was to treat TB first and see whether CD4 cell counts increased. Others felt however, that CD4 cell testing takes time and represents an additional barrier to getting onto ART — and for many people with TB and HIV, there is little time to waste.

One participant from India said that her personal preference would be to complete TB treatment first, given the potential for toxicity and the drug interactions between rifampicin and many ARVs.

The group recommended that people on TB treatment who start ART do not use a nevirapine regimen but rather an efavirenz-based or triple nucleoside based regimen. Unfortunately, time was too short to go into

what the optimum ART regimen would be to use in pregnant women on TB treatment, or how to manage people who are on second-line protease inhibitor based regimen.

There was also some brief discussion on the management of active Hepatitis B virus (HBV) in people with HIV. The drugs used in the treatment of HBV (3TC, FTC and tenofovir) are also ARVs. ART treatment may thus need to be given earlier in people with both active HBV and HIV since giving these drugs as mono or dual therapy may lead to HIV drug resistance.

Conclusion

This meeting represented the first of several opportunities for PLHIV, and participants in the meeting were urged to go back to their communities to gather further input.

“We are giving this input or perspective from the PLWAs perspective, or people living with HIV/AIDS themselves, rather than waiting for the researchers and the managers and the bureaucrats to decide what the guidelines should look like,” said Dubela.

PLHIV emphasized that the revised ART Guidelines “need to push the envelope,” one said, “like when they first came out.” Issues of cost and access will indeed need to be worked out — but that is a role for the activist community.

At the same time, PLHIV want care and treatment programmes of the highest quality, but they also prefer them to be as simple and unobtrusive as possible. They don’t want programmes to require people who are stable on treatment to come into the clinic too often unless it is absolutely necessary. They don’t want unnecessary and overly complicated treatment. Finally, they would prefer that programmes to place more emphasis on the individual’s holistic needs rather than treating them just as a patient or even worse, someone who must be kept from spreading HIV.