8. PHASING OUT STAVUDINE: PROGRESS AND CHALLENGES

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 9 – Guidance on operations and service delivery

Key message
- Countries should discontinue initiating new people on d4T-containing regimens and accelerate the pace of phasing out the use of d4T in people who have already initiated ART.

Introduction
In 2010, WHO guidelines for antiretroviral therapy (1) recommended that countries take steps to progressively reduce the use of stavudine (d4T) because of its well-recognized toxicity. This recommendation was supported by a WHO technical brief issued in 2010 (2) that outlined several guiding principles for phasing out d4T.

Since that time, most countries have moved towards phasing out d4T, but progress is varied and consumption overall remains high. At the same time, there is a growing appreciation of the need to move towards standardized, more tolerable and robust regimens to support the next phase of scaling up of antiretroviral therapy (ART). In 2013 WHO issued consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (3) that further simplify the regimen choices for all groups of people living with HIV.

This section provides an overview of the evidence supporting the 2010 d4T phaseout recommendation, outlines progress to date and summarizes the main challenges and potential solutions for countries to reach the goal of completely phasing out the use of d4T in first-line ART.

Why phase out d4T use?
The fact that d4T use is associated with important types of toxicity has been known for some time. WHO guidelines for antiretroviral therapy as early as 2003 recognized that among the nucleoside reverse-transcriptase inhibitors (NRTIs), d4T was most consistently associated with metabolic toxicity and long-term complications, in

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**Fig. 8.1. Trends in antiretroviral drug prices, 2006 and 2012**

![Graph showing trends in antiretroviral drug prices](image)

particular lipoatrophy, peripheral neuropathy and lactic acidosis. Since that time, an accumulation of evidence and experience from resource-limited settings has highlighted the problems associated with d4T use within a simplified public health approach to scaling up ART (4–8). Nevertheless, the low cost and simplicity of d4T-containing regimens led to it becoming one of the most widely used ARV drugs, with over half of all people taking first-line ART in low and middle-income settings receiving d4T in 2010 (2).

In late 2006, WHO issued advice recommending that countries switch to a lower dose of d4T (30 mg) as a way to minimize side effects. Although this lower dose resulted in some improvement (5), the overall frequency of side effects remains high and increases with longer use of the drug (4,9). An accumulation of evidence from low- and middle-income countries has demonstrated the negative programmatic effects of d4T toxicity in terms of increased regimen substitution, treatment interruption, suboptimal adherence and the need for expert clinical supervision. This evidence, combined with the substantial price reductions in ARV drugs in recent years, has reinforced the imperative to replace d4T with less toxic alternatives, such as tenofovir (TDF), in first-line antiretroviral therapy (Fig. 8.1).

Risk of severe and life-threatening toxicity

The 2010 WHO recommendation was based on the acknowledgement that cumulative exposure to ART has the potential to cause disfiguring, painful and life-threatening side effects, such as lipodystrophy, peripheral neuropathy and lactic acidosis (10,11), often associated with long-term d4T use (12). Similar safety concerns exist for adolescents, children and infants. In Europe and the United States, d4T use has declined sharply during the past decade (13), and its use today is restricted to people for whom there are no appropriate alternatives and for the shortest possible time (11).

Increased regimen switches

d4T is associated with the highest rate of toxicity-driven substitutions (14) of all ARV drugs, which can be more than 10 times higher than for most other ARV drugs (15). In South Africa, 21% of the people taking d4T had changed to another drug within three years due to symptomatic hyperlactataemia (5%), lipodystrophy (9%) or peripheral neuropathy (6%) (16). In Lesotho, people taking d4T were almost six times more likely to experience a toxicity-driven switch than people taking TDF (17). In Botswana, treatment-modifying toxicity strongly predicted death and was most commonly associated with d4T regimens (18). In Cambodia, more than 90% of the people taking d4T had switched from it within six years of initiating therapy due to toxicity (19), mainly due to lipoatrophy (8).

Suboptimal adherence and treatment interruptions

Drug toxicity is a recognized cause of non-adherence to medication (20). A systematic review of barriers to adherence reported by medication users found that 11% stated that side effects were a barrier to adherence, and 12% reported that complicated regimens were challenges to adherence (21). d4T use has specifically been associated with increased likelihood of non-adherence (22,23) and defaulting from care (24). In addition, drug-related toxicity is the leading cause of treatment interruption, accounting for more than one third of all treatment interruptions reported in a systematic review of the issue (25).

Limited monitoring capacity

It has been suggested that d4T use could be continued with close monitoring of toxicity to save drug costs. However, the high rates of regimen substitution suggest that this is not cost-effective in the long run. Moreover, capacity for toxicity monitoring remains limited in many settings with a high burden of HIV. A study from Malawi found substantial underreporting of side effects, suggesting that the true incidence of toxicity of d4T in clinical practice may be underreported (26).

Limited monitoring capacity has also been reported as a reason for the slow phasing out from d4T to preferred regimens. In Lesotho, patients in health centres were more than twice as likely to be receiving a d4T-based regimen compared with those in hospitals, and this was partly explained by the challenge of assessing baseline creatinine before switching people from d4T to TDF (27) (despite this not being a requirement according to WHO guidelines (3)). Another report, also from Lesotho (28), found that use of d4T decreased significantly once nurses were provided with simple algorithms to support the management of TDF; the use of TDF instead of d4T was found to facilitate task shifting and decentralization, since less clinical management was required.

Earlier initiation of ART

Risk–benefit considerations for providing ARV drugs to people earlier in the course of their disease need to take into account the potential harm of exposing people to medicine toxicity (29). Following a systematic review of the evidence regarding morbidity and mortality, the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (3) now recommend that countries move towards earlier initiation of ART for clinical benefit, at CD4 <500 cells/mm³. These considerations become even more important when the main reason for initiating therapy is not for the person’s own health but to prevent HIV transmission to others. An
accumulation of evidence in the last few years has led to WHO recommendations for preventing HIV transmission in serodiscordant couples even at higher CD4 counts and preventing mother-to-child transmission and has been suggested for other groups at high risk of HIV infection (30). Several countries are already in the process of revising initiation criteria to include treatment-as-prevention options. Earlier treatment, which leads to longer exposure to ARV, when considered, should be coupled with a move to less toxic regimens.

Progress in phasing out d4T use to date

In higher-income settings, where regimen choices and resources are greater, d4T use has been progressively reduced during the past decade. Between January 2005 and March 2010, an estimated 56 000 people were exposed to d4T in Europe (Fig. 8.2). This is less than the total number of people initiating d4T in Zambia in 2011 (64 552) and highlights the fact that d4T use has largely been confined to resource-limited settings for many years.

Fig. 8.2. d4T use declines in Europe, 2006–2010

![Graph showing d4T use declines in Europe, 2006–2010](image)


Fig. 8.3. Countries reducing d4T use >50% between 2010 and 2011

![Graph showing countries reducing d4T use >50% between 2010 and 2011](image)

Since 2010, most countries have reduced the proportion of people initiating d4T-based regimens. However, the rate of change has differed markedly in different countries. Fig. 8.3 and 8.4 show the change in use of d4T in some key countries between 2010 and 2011. Some countries (such as Cameroon, Kenya and Zambia) made further progress in phasing out d4T in 2012, but in a few countries with a high burden of HIV, d4T continues to be prescribed to substantial numbers of people, and the continued scaling up of treatment has meant that, overall, the absolute number of people initiating d4T in 2011 increased compared with 2010.

![Fig. 8.4. Countries reducing d4T use <50% between 2010 and 2011](image)

Despite progress, in 2011, 1.1 million people newly initiated d4T-based first-line regimens, the vast majority in resource-limited settings in Africa with a high burden of HIV infection.

### Overcoming challenges to phasing out d4T

Several countries have reported barriers to phasing out d4T. These include: the high cost of AZT or TDF compared with d4T (31), uncertainties regarding whom to give priority to for phaseout (32), the need for donor support (33) and the need to reduce stockpiles of d4T (32).

### Higher cost of alternative drugs

The speed of transition away from d4T has mainly been limited by the higher cost of the alternative drugs AZT and TDF. However, the cost of TDF-based regimens has declined substantially. The best available price for TDF globally has dropped from US$ 365 per person per year in 2005 to US$ 57 in 2012; similarly, the cost of TDF-combinations recommended by WHO for first-line therapy have all declined substantially in recent years (Fig. 8.5) (34).
Although d4T remains the most affordable drug in terms of absolute cost, several studies have concluded that a switch away from d4T-based regimens is cost-effective if health service costs associated with managing side effects are considered. A study from South Africa concluded that d4T use was not cost-effective due to decreased quality-adjusted survival (35). Similar results have been reported from Lesotho (36) and India (37). In Myanmar, the higher cost of TDF was offset by the reduced need for laboratory tests and clinic visits (38).

Uncertainty regarding which people to give priority to for phaseout

Several countries face the challenge of transitioning a large number of people from d4T, raising questions of who should take priority. From a clinical perspective, people with d4T related side effects and those coinfected with hepatitis B virus are most clearly going to benefit from an immediate switch to TDF (given the anti-hepatitis B virus properties of this drug). Beyond these two groups of people, there is no strong rationale for favouring certain groups over others, and while incremental phaseout may be necessary based on operational and feasibility considerations, the goal should be to move entirely away from d4T use and reserve it for use only in exceptional situations.

Funding the switch

Recently, the Global Fund for AIDS, Tuberculosis and Malaria and the United States President’s Emergency Plan for AIDS Relief have clearly committed to supporting countries in moving away from d4T. Programmes supported by the United States President’s Emergency Plan for AIDS Relief already report a sharp decrease in the purchase of d4T in the past few years (39). Existing donor grants have already been reprogrammed in several countries with a high burden of HIV, and this will facilitate phaseout.

To facilitate phaseout, countries should develop national plans that identify key priority groups for immediate change and include timelines for subsequent phaseout. The overall operational plan for phaseout should be costed, including estimates of additional domestic and external resources required to fund the switch.

Stockpiles of d4T

Stockpiles of d4T exist in several countries and are a major reason for slow phaseout. This challenge has been confronted in other disease areas: for example, when countries were recommended to shift away from chloroquine towards artemisinin-based combination therapy for treating
malaria (40). Several countries used chloroquine stockpiles as buffers for delays in artemisinin-based combination shipments or in cases of stock-outs while progressively introducing artemisinin-based combination therapy into clinics across the country. Similarly, WHO recommends discontinuing ordering d4T-based formulations and that national stakeholders determine the future use of remaining stockpiles; one solution would be to reserve stocks for back-up situations for individuals who may require d4T in the absence of alternative choices.

Preferred ARV drugs for replacing d4T
The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (3) give preference to TDF over AZT for first-line ART regimens based on an accumulation of evidence and experience. Although both TDF and AZT are associated with toxicity, in countries in which both regimens have been used, TDF has been found to be the better tolerated regimen. AZT, like d4T, is a thymidine analogue, and although it is better tolerated than d4T, it has similar known metabolic and mitochondrial toxicity (17,41). In Uganda, among people changed to AZT because of d4T toxicity, 6.6% subsequently had to be changed to TDF (3.4% because of anaemia and 3.1% because of failure) (42). A review comparing TDF and AZT in first-line therapy found that TDF was superior in immune response and adherence, and resistance emerged less frequently (43). Several studies (44,45) have assessed the comparative cost–effectiveness of WHO-recommended TDF and AZT-based first-line options and concluded that TDF is cost-effective (46,47).

Finally, for people already receiving first-line therapy, switching from d4T to TDF is preferred over AZT when considering the potential for cross-resistance of mutations that are known to accumulate among people exposed to d4T (48). A recent analysis of resistance mutations associated with d4T-containing ART from 35 cohorts (49) concluded that, in settings in which genotype resistance testing is not available, TDF is more likely to be effective than AZT.

Phasing out d4T among children
There has been some suggestion that d4T toxicity is less severe in children than adults. Studies from Uganda (50) and Cameroon (51) found no difference in the frequency of adverse events among children, comparing AZT- and d4T-based regimens. Nevertheless, about one third of the children experienced an adverse event on either regimen. Lipodystrophy was the most commonly reported adverse event, similar to other African cohorts (52).

Until recently, concern about the limited number of formulations for children provided a potential justification for continuing to support d4T use in children. However, the number of approved formulations for children has increased in recent years, and with the recent approval of TDF for children ≥2 years, all NRTIs currently in use for adults are available for use among children. There is no longer a rationale for making different recommendations for children versus adults. This alignment of regimens as much as possible between children and adults to further simplify treatment has been endorsed through the treatment recommendations in the 2013 WHO guidelines (3). Therefore, although d4T may be of use for individual children, as for adults, overall the WHO advice to phase out d4T applies equally to adults and children alike.

Phasing out other ARV drugs
Through the Treatment 2.0 strategy, WHO is promoting the rationalization of first-line ART to simplify procurement and prescribing and maximize health service efficiency. The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (3) further simplify options by promoting a single, preferred first-line regimen based on TDF + XTC + EFV for adults and older children (>3 years).

According to data from the WHO sixth annual survey on the use of ARV drugs and diagnostics, the number of first-line ART regimens per country ranged from 4 to 38. In some regions, countries continue to procure ARV drugs that are no longer recommended as preferred options, such as indinavir, saquinavir and fosamprenavir (53).

Although it is important to retain alternative regimens in case of poor tolerability or contraindications, countries are encouraged to develop phaseout plans for other drugs that may no longer be preferred to simplify and standardize first- and second-line ART as far as possible.

Conclusions
Since 2010, WHO has recommended that countries phase out d4T in favour of less toxic regimens. During the past two years, progress on phasing out d4T has been variable, with some countries making rapid and substantial progress and others taking a phased approach. Although countries face different barriers to phaseout, WHO recommends that countries discontinue initiating new people on d4T-containing regimens and accelerate the pace of phasing out d4T use in people already receiving ART, particularly the countries in which d4T remains the main first-line option and in which policies of earlier initiation of ART are being implemented.
9. TRANSITION TO NEW HIV TREATMENT REGIMENS – ISSUES RELATED TO PROCUREMENT AND SUPPLY CHAIN MANAGEMENT

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 9 – Guidance on operations and service delivery

This section was developed to advise a phased approach to implementing partners, antiretroviral therapy programme managers, procurement managers and other relevant parties. The ultimate purpose is to ensure a continuous supply of antiretroviral (ARV) drugs and to ensure rapid and efficient implementation of the new WHO HIV treatment guidelines, with smooth transitioning to new recommended ARV regimens, while reducing the wastage or expiry of products that are no longer recommended.

Background

WHO’s recent consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (1) recommend a preferred treatment regimen based on tenofovir (TDF) in combination with lamivudine and efavirenz (TLE), or TDF with emtricitabine and efavirenz (TEE), preferably as fixed-dose combinations. Comparative systematic reviews showed that these two regimens are associated with less risk of severe adverse events and better antiviral and treatment response compared with other once- and twice-daily options currently available. Evidence also indicates that EFV has superior efficacy and tolerability to NVP, including when combined with TDF + 3TC (or FTC) as a once-daily regimen. In addition, WHO recommends that countries discontinue stavudine (d4T) as a preferred first-line option, because of its cumulative mitochondrial toxicity. The implementation of these new recommendations implies transition of the nearly 1 million people who were still receiving d4T at the end of 2012 to tenofovir-based regimens. A decision on how to deal with the 2 million to 4 million people who received zidovudine (AZT)-containing regimens and the 4 600 000–5 800 000 people receiving NVP-containing regimens is needed. As has been seen with previous regimen changes, any such major transition is a significant undertaking that requires careful procurement and supply chain management planning, coupled with clear guidance to inform prescribing practices.

The recommendations in support of option B+ in preventing mother-to-child transmission and adult treatment initiation at a CD4 count of 500 cells/mm³ or lower, will also potentially increase the demand for ARV drugs.

Challenges

Three key challenges face the supply chain with these new recommendations.

1. The currently approved suppliers of fixed-dose combination formulations of TEE and TLE expect that their production capacity will be sufficient to satisfy the increased demand for these formulations in 2014, as in 2013 new capacity to produce TLE and TEE has been brought on line. However, in the short term, their supply is still constrained, since buffer stocks held by countries that switched to TDF-based first-line treatment have not been built up yet.

2. At present, order to delivery lead times for TEE and TLE formulations are averaging 4–8 months, including manufacturing time and delivery to country.

3. Purchasers and implementing partners with people receiving d4T-, AZT-, and NVP-based regimens have stocks and orders in process that should be considered in the transition process to avoid the occurrence of stock-outs and also wastage or expiry of usable products.

Recommendations

Programmes should plan carefully and discuss with their suppliers the pace at which increased quantities of TDF- and EFV-based products can be made available. This will require a graduated process of transition. To ensure that supply is available to meet anticipated demand, a phased programme is highly recommended. Suggested approaches are the following.

1. Initiate new people eligible for antiretroviral therapy on TDF-based regimens, with preference for the fixed-dose combinations of TLE or TEE.

2. Transition people currently receiving d4T-based regimens to a TDF-based regimen:

   • For people with clinical evidence of d4T-related toxicity: immediate replacement with TEE or TLE is recommended.

18. Either approved or tentatively approved by the United States Food and Drug Administration or prequalified by WHO.
For people with evidence of treatment failure, shift to second-line treatment with TDF + 3TC or TDF + FTC plus LPV/r or ATV/r as recommended by the 2013 WHO guidelines (1).

For people with minimal or no d4T-related toxicity, replace the d4T-based regimen with TEE or TLE as soon as possible, in a phased programme to enable the use of current d4T stocks and orders. No new procurement orders of d4T-based formulations should be planned.

3. People currently receiving AZT- and/or NVP-based regimens to TEE or TLE should be transitioned in a phased programme to enable the use of current stocks and orders and taking into account the speed at which increased deliveries of TDF products can be ordered and delivered; in practice, it is suggested that national ART programmes consider the following sequence.

For people with evidence of treatment failure, shift to second-line therapy with TDF + 3TC (or TDF + FTC) plus LPV/r or ATV/r (with monitoring of renal function) as recommended by the 2013 WHO consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection (1).

For people with clinical evidence of AZT-related or NVP-related toxicity, immediate change to TEE or TLE is recommended. New procurement orders of AZT- or NVP-based formulations should be planned only in the context of alternative first-line and/or second-line therapy needs.

For people developing TB while being treated with AZT + 3TC + NVP, switch to TLE or TEE immediately, since NVP is not recommended as a preferred option and using TEE or TLE reduces the pill count and increases adherence to HIV and TB treatment.

For people without toxicity or treatment failure, replace with TEE or TLE as soon as possible. AZT is also associated with mitochondrial toxicity that can emerge more slowly than with d4T. EFV is clinically superior to NVP in terms of suppression of viral load and length of time to treatment failure; people taking an EFV-based regimen were also more likely to achieve antiviral success. In the absence of treatment failure, switching to a regimen containing TDF and EFV is not detrimental from the perspective of developing HIV drug resistance.

It should also be recognized that not all countries can transition at the same time or at the same pace and that they also differ in other aspects. In areas with a high prevalence of HIV-2 infection, for example, the procurement and use of two-drug fixed-dose combinations (TDF with 3TC, TDF with FTC and AZT with 3TC) might still be a preferred option, since this provides flexibility to combine the NRTI backbone with protease inhibitors in first-line therapy for people living with HIV-2. Advice on these challenges and on how countries and programmes can coordinate their transitions and product requirements is available from:

- WHO: AIDS Medicines and Diagnostic Service: Vincent Habiyambere (habiyamberev@who.int);
- United States of America Government: Supply Chain for Health Division, Office of HIV/AIDS at the United States Agency for International Development: Christine Malati (cmalati@usaid.gov), Mike Hope (mhope@usaid.gov) or for questions USGTx@usaid.gov;
- the Global Fund to Fight AIDS, Tuberculosis and Malaria: Martin Auton (Martin.Auton@theglobalfund.org) or Ade Fakoya (ade.fakoya@theglobalfund.org); and
- UNITAID: Taufiqur Rahman (rahmant@unitaid.who.int).

Conclusions

The transition to the new regimens will ensure that people receive the most effective treatment. This transition can be achieved if it is well planned and coordinated. Full transition cannot happen in all countries and across all groups of people living with HIV immediately, but the constraint on the supply side for the new TDF- and EFV-containing formulations has progressively become less critical. However, since their supply is still somewhat constrained, it is important to ensure that people do not risk treatment interruption. To achieve a smooth transition in as short a time as possible, without treatment interruption, significant collaboration between programme managers and their suppliers is essential.
10. TRANSITION TO 2013 WHO ANTIRETROVIRAL THERAPY REGIMENS FOR CHILDREN – PROCUREMENT AND SUPPLY CHAIN MANAGEMENT ISSUES

Key messages

• When available, age-appropriate fixed-dose combinations for any regimen are preferable for children.

• Oral liquid formulations should be avoided in favour of solid oral dosage forms when available.

• Dispersible tablets (also known as tablets for oral solution) are the preferred solid oral formulations.

• Fixed-dose combinations of ABC + 3TC (60 mg + 30 mg) in both dispersible and non-dispersible scored tablets are available. The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children (IATT) lists the dispersible formulation as the preferred option.

• Two formulations of LPV/r are available for use among young children: LPV/r 100 mg/25 mg heat-stable tablet for children >10 kg who are able to swallow whole tablets, and LPV/r oral liquid 80/20 mg per 1 ml for use among infants.

• Country programmes are urged to limit the procurement of ARV products for children to formulations included on the Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children.

Context

The WHO 2013 consolidated guidelines recommend preferred and alternative first-line ARV regimens for children as well as second-line regimens. In addition, although the guidelines in general recommend once-daily fixed-dose combinations, when possible, to facilitate procurement and supply chain management logistics, as well as adherence, additional logistic and programme factors should be addressed for national programmes to select optimal formulations. To ensure smooth implementation of the recommended first-line regimens for children and adolescents, it is critical for policy-makers and implementers to consider the availability of ARV formulations for children when determining appropriate specific drug formulation recommendations for children.

General principles in the selection of ARV products for children include age-appropriate fixed-dose combinations for any regimen when such a formulation is available. Oral liquid formulations should be avoided in favour of solid oral dosage forms when available; dispersible tablets (also known as tablets for oral solution) are the preferred solid oral formulations.

In light of continuing challenges of ensuring availability of ARV formulations for children, the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children provides guidance on optimal ARV products for children to promote a secure and sustainable supply. The group met in September 2013 to revise and update the 2011 Optimized Paediatric ARV Formulary (2); Annex 10.1 presents an updated formulary.

Update of the availability of ARV formulations for children

Formulations of ABC for children containing fixed-dose combinations

a) ABC is now included among the preferred non-nucleoside reverse-transcriptase inhibitors (NRTI) for first-line ART among children younger than three years and as the preferred NRTI for children 3–10 years old in combination with lamivudine (3TC) and either LPV/r, nevirapine (NVP) or efavirenz (EFV).
b) Currently there are fixed-dose combinations of ABC + 3TC (60 mg + 30 mg) in both dispersible and non-dispersible scored tablets. The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children lists the dispersible formulations as the preferred option.

c) To provide a complete regimen, the ABC + 3TC fixed-dose combinations must be combined with a suitable formulation of NVP, EFV or LPV/r.

Formulations of TDF for children

a) TDF is now approved by stringent national pharmaceutical regulatory agencies, including the United States Food and Drug Administration for use among children older than two years of age.

b) WHO recommends TDF-containing regimens as an alternative first-line regimen for children 3–10 years of age and as a preferred first-line regimen for adolescents older than 10 years and weighing more than 35 kg (in alignment with preferred first-line regimens for adults).

c) A TDF-containing fixed-dose combination for children is currently not available.

d) TDF is available in three different formulations for children for use across different weight bands. The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children lists the dispersible formulations as the preferred option (Table 10.1).

d) At present, TDF formulations must be combined with two additional single-component ARV formulations to achieve a complete regimen for people weighing less than 35 kg. This will significantly complicate the use of TDF-based regimens among children until a suitable fixed-dose combination becomes available.

Table 10.1. TDF dosing using currently available formulations for children

<table>
<thead>
<tr>
<th>Weight band</th>
<th>10–13.9 kg</th>
<th>14–19.9 kg</th>
<th>20–24.9 kg</th>
<th>25–29.9 kg</th>
<th>30–34.9 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>3 powder scoops</td>
<td>One 150-mg tablet</td>
<td>One 200-mg tablet</td>
<td>One 200-mg tablet</td>
<td>One 300-mg tablet</td>
</tr>
</tbody>
</table>

Formulations of LPV/r for children

a. WHO strongly recommends the use of LPV/r as part of first-line ART for all children living with HIV younger than three years.

b. Only two formulations of LPV/r are currently available for use among young children.

a. There is a LPV/r 100 mg/25 mg heat-stable tablet for children >10 kg who are able to swallow whole tablets. These tablets must be swallowed whole and must not be chewed, crushed or dissolved.

b. LPV/r oral liquid 80/20 mg per 1 ml can be used for infants; however, this has poor palatability and is not heat-stable. LPV/r oral liquid 80/20 mg per 1 ml should be shipped and stored between 2°C and –8°C. After dispensing, storage at 2–8°C is preferred, but the product can be kept at up to 25°C for up to two months.

c. Although new formulations are being developed, the time between regulatory approval and product availability in specific countries is unpredictable. Once the product obtains regulatory approval from a stringent regulatory authority, the steps for manufacturing commercial batches, adoption into national guidelines, national regulation and procurement processes must be taken into account.

Drugs being phased out

Didanosine (ddl)

a. ddl is no longer recommended as an alternative NRTI in adult or child second-line regimens because of toxicity, lower efficacy and inconvenient dosing requirements.

b. Countries should transition people currently receiving ddl to more optimal regimens as soon as possible. For example, 3TC can replace ddl in WHO-recommended second-line regimens.

19. This formulation has been referred to as a “sprinkle” or “minitab”.

**Stavudine (d4T)**

a. d4T is no longer recommended for adults or children except in special circumstances in children when AZT cannot be used due to toxicity and ABC is not available.

b. Countries should transition people currently receiving d4T-based regimens to more optimal regimens as soon as possible.

**Conclusions**

The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children has been updated based on the WHO 2013 consolidated guidelines. Countries are encouraged to limit the procurement of ARV drugs for children to the products listed on the Optimized Paediatric Formulary to simplify the supply chain and aggregate global demand to stabilize global supply of ARV drugs for children.

**ANNEX 10.1.**

Optimal and limited-use lists of ARV formulations for children

### Optimal

<table>
<thead>
<tr>
<th>Drug class (or fixed-dose combination)</th>
<th>Product</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Rationale for being on the list</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>AZT</td>
<td>Oral liquid</td>
<td>50 mg/5 ml</td>
<td>For use in preventing mother-to-child transmission</td>
</tr>
<tr>
<td>NNRTI</td>
<td>EFV</td>
<td>Tablet (scored)</td>
<td>200 mg</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>NVP</td>
<td>Tablet (dispersible, scored)</td>
<td>50 mg</td>
<td>For use in preventing mother-to-child transmission</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>LPV/r</td>
<td>Oral liquid</td>
<td>80 mg/20 ml</td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>AZT + 3TC</td>
<td>Tablet (dispersible, scored)</td>
<td>60/30 mg</td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>AZT + 3TC + NVP</td>
<td>Tablet (dispersible, scored)</td>
<td>60/30/50 mg</td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>ABC + 3TC</td>
<td>Tablet (dispersible, scored)</td>
<td>60/30 mg</td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>ABC + 3TC + AZT</td>
<td>Tablet (non-dispersible, scored)</td>
<td>60/30/60 mg</td>
<td></td>
</tr>
</tbody>
</table>

### Limited-use

<table>
<thead>
<tr>
<th>Drug class (or fixed-dose combination)</th>
<th>Product</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Rationale for being on the list</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>3TC</td>
<td>Tablet (dispersible)</td>
<td>30 mg</td>
<td>To be used with TDF single formulation</td>
</tr>
<tr>
<td>NRTI</td>
<td>TDF</td>
<td>Oral powder*</td>
<td>40 mg/scoop</td>
<td>For use in special circumstances when ABC or AZT cannot be used or for people with hepatitis B, until an appropriate fixed-dose combination becomes available</td>
</tr>
</tbody>
</table>

*Product is administered as an oral powder, not reconstituted with liquids.*
<table>
<thead>
<tr>
<th>Drug class (or fixed-dose combination)</th>
<th>Product</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Rationale for being on the list</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>TDF</td>
<td>Tablet</td>
<td>150 mg</td>
<td>See above</td>
</tr>
<tr>
<td>NRTI</td>
<td>TDF</td>
<td>Tablet</td>
<td>200 mg</td>
<td>See above</td>
</tr>
<tr>
<td>NNRTI</td>
<td>ETV</td>
<td>Tablet</td>
<td>25 mg</td>
<td>Special circumstance in third line where appropriate</td>
</tr>
<tr>
<td>NNRTI</td>
<td>ETV</td>
<td>Tablet</td>
<td>100 mg</td>
<td>See above</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>RTV</td>
<td>Oral liquid</td>
<td>400 mg/5 ml</td>
<td>For boosting of non-co-formulated protease inhibitors and super-boosting protease inhibitors during TB coinfection</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>ATV</td>
<td>Solid oral dosage form</td>
<td>100 mg</td>
<td>Use in alternative second line for children older than six years old when boosting with separate RTV is available</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>ATV</td>
<td>Solid oral dosage form</td>
<td>150 mg</td>
<td>See above</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>DRV</td>
<td>Tablet</td>
<td>75 mg</td>
<td>Special circumstances in third line where appropriate and when boosting with separate RTV is available</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>RAL</td>
<td>Chewable tablet (scored)</td>
<td>100 mg</td>
<td>For use in third line where appropriate</td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>d4T + 3TC + NVP</td>
<td>Tablet (dispersible, scored)</td>
<td>6/30/50 mg</td>
<td>Special circumstances where people cannot be transitioned to a preferred or alternative NRTI</td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>d4T + 3TC</td>
<td>Tablet (dispersible, scored)</td>
<td>6/30 mg</td>
<td>See above</td>
</tr>
</tbody>
</table>
11. COMMUNITY-BASED DELIVERY OF ANTIRETROVIRAL THERAPY

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 9 – Guidance on operations and service delivery.

Key messages

- Community-based models of ART delivery can benefit people living with HIV and decongest facilities in settings with a high burden of HIV infection.
- There is no one-size-fits-all approach to community models of ART delivery. The context in which they operate is important, and models need to be flexible and responsive to the needs of people living with HIV.
- Bidirectional referral is essential so that people in stable condition can be moved out of the clinic into the community and those who experience health problems can be referred back to facility care.
- A conducive national policy and regulatory framework around providing ARV drugs is essential to the success of community-based ART delivery.
- Countries should consider measures to retain and enhance the performance of community-based staff with new or increased responsibilities.
- Simplified, integrated monitoring and evaluation systems are necessary to ensure the success of community-based models.

Background

During the past decade, antiretroviral therapy (ART) has been scaled up, and this has been particularly rapid in low- and middle-income countries – growing from 300 000 people in 2002 to 9.7 million by the end of 2012 (1). The greatest scale-up of ART happened in sub-Saharan Africa. By the end of 2012, more than 7.5 million people in the region were accessing ART, an increase of more than 90% since the end of 2009 (2).

In addition to the need for continued scale-up of access to ART, there is growing emphasis to improve the retention of people who have already initiated treatment. In most settings, HIV programmes are faced with the challenges of retaining a growing number of people in care. Retention is a challenge in all stages of the HIV care cascade, from HIV testing to long-term treatment (3,4). There is increasing recognition that attrition is threatening the effectiveness of ART programmes and is growing in some settings. For ART programmes to continue to expand while retaining people in care and achieving high level of treatment adherence, novel models of service delivery are needed.

Reflecting the need to respond to these challenges, the WHO 2013 guidelines (5) recommend decentralized HIV treatment delivery with initiation of ART at peripheral health facilities and the option of maintenance treatment at community level and task shifting to include trained and supervised community health workers to dispense ART between regular clinic visits. With the expansion of access to ART and sustained adherence, people living with HIV can expect a near normal life expectancy, including in resource-limited settings. To support lifelong care, there is a growing realization that, for most people receiving treatment, models of service delivery need to be adapted to support the management of HIV as a chronic condition. Out-of-clinic or community-based models of care show great promise in supporting adherence and retention for lifelong ART. There is no one-size-fits-all approach to community models of ART delivery. The context in which they operate is important and models need to be flexible and responsive to the needs of people living with HIV.

WHO held a consultative meeting on community ART delivery in eastern and southern Africa from 5–7 December 2013 in Cape Town, South Africa. This update is based on this consultation and developed to advise national programmes and their stakeholders in settings with a high burden of HIV on implementation considerations for community-based ART delivery and share some lessons learned. The target audience is national policy-makers and HIV programme managers, health care providers and other relevant stakeholders. The main purpose is to support country programming and scale-up by describing key operational and programmatic considerations for effective and sustainable community-based ART delivery. WHO is currently consolidating guidance for key populations.

Evidence for WHO recommendations

Growing evidence indicates that decentralized models of HIV care can provide ART services comparable to those in hospital-based settings. A systematic review on the impact
of decentralization on ART delivery identified evidence that people who initiated ART at a hospital and maintained at a health centre were more likely to be retained in care than people initiating and maintained at the hospital level (overall estimate RR 1.12, 95% CI 1.08–1.17). The review from cluster randomized controlled trials shows moderate quality of evidence, with similar mortality rates at 12 months (RR 1.03, 95% CI 0.64–1.65) for maintenance ART delivered at the health facility or in the community. The risk of mortality did not differ significantly at six months (RR 1.44, 95% CI 0.81–2.57) and 24 months (RR 1.50, 95% CI 0.91–2.47) in the cohort study. Comparable attrition (overall RR 1.01, 95% CI 0.99–1.03) was observed after 12 months in two trials with ART maintenance in the community [6]. Fig 11.1 summarizes the pooled relative risk for retention by model of decentralization.

These studies are supported by similarly positive outcomes reported by programmes piloting community ART delivery. Another review, assessing models that engage laypeople in ART delivery, indicates that such programmes can overcome barriers to retention and decongest health facilities with a high disease burden [7,8].

**Programmatic and implementation considerations**

More and more programmes in sub-Saharan Africa are exploring innovative community ART delivery models, which aim to remove some of the structural and economic barriers to accessing facility-based HIV services. Such models of ART delivery have led to a shift away from primarily specialized (hospital-based) service delivery models to (1) decentralize ART to primary health facilities, with concomitant task-shifting, expansion and strengthening of links to community systems; and (2) out-of-clinic models of HIV treatment that engage community providers in essential tasks, including ART distribution, peer adherence and social support to supplement conventional models of ART delivery, particularly in settings where shortages of care providers create bottlenecks in service delivery [9–11]. Annex 11.1 summarizes selected models of community ART delivery and with corresponding outcomes where available.

Several programmatic and implementation considerations are common to the successes reported by community-based models of ART delivery:

- community-based ART services delivered as an extension of facility-based ART services;
- a reliable and flexible ARV drug supply system;
- appropriate human resources; and
- adapted monitoring and evaluation linked to facility-level information systems to tracking input and outcomes.

**Community-based ART delivered as part of facility or clinic ART services**

Community-based models of ART delivery are designed to benefit service users and health care delivery systems, and as such there is substantial overlap in strengthening health systems and community systems. Community ART delivery needs input from and linkage with health facility staff, people living with HIV and communities at large. Flexibility is therefore necessary for people living with HIV to move along the care pathway between facility- and community-based models. Strengthening systems

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**Fig. 11.1. Summary of decentralization and retention in care**

<table>
<thead>
<tr>
<th>Partial N = 39 090</th>
<th>Full N = 56 360</th>
<th>Community-based N = 709</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.20</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>1.10</td>
<td>1.05</td>
<td>1.05</td>
</tr>
<tr>
<td>1.00</td>
<td>0.95</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Source: Suthar et al. [12].
for bidirectional patient referral is essential, such that stable people living with HIV can be moved out of the clinic into the community, while those who experience health problems are efficiently and timely referred back to clinical care. In addition, packaging community-based ART services as an extension of the facility will ensure clinical and programme accountability. Community models of ART delivery are not a replacement of facility-level care but complementary services. People living with HIV in the community model must feel welcomed in clinic settings, and involvement of respective facility staff (in designing and implementing community ART delivery models) is necessary to ensure a supportive environment. They have increased capacity for peer support and community involvement, which can facilitate improved retention in care and support for people living with HIV.

Reliable and flexible drug supply system

The success of models of community ART delivery depends on reducing the workload for both people living with HIV and providers by allowing for longer dispensing intervals and for community workers to dispense ARV drugs between clinic visits. A conducive national regulatory environment around the provision of ARV drugs is therefore essential to the success of community-based ART delivery. Countries and national regulatory bodies need to address policy and regulatory frameworks for who can dispense or distribute ARV drugs, the frequency required for ART prescription and who can refill ART prescriptions.

Appropriate human resources

Community ART models of care may help alleviate the workload of clinical teams but require additional work by some cadres of health workers, usually trained community health workers or “lay” providers. Health workers and staff involved in community-based ART services need to be appropriately supported, both in terms of training, supervision, management and incentives and remuneration. Since community-based models are an extension of facility services, they often require task shifting or task sharing. Successful models have included ways to ensure appropriate recognition for those involved as well as management systems that support the community-based ART delivery. In many settings, “lay” cadres and community health workers may be under different regulatory frameworks than health professionals and are mostly funded through short-term projects. This often leads to gaps in sustainability and contributes to high attrition of health workers. WHO recommends that countries consider measures such as financial and/or non-financial incentives, performance-based incentives or other methods as means by which to retain and enhance the performance of health workers with new or increased responsibilities, commensurate with available resources in a sustainable manner (13).

People living with HIV play a key role in delivering ART at the community level, including acting as role models to others who need HIV treatment and providing peer support, which in some cases contributes to reducing stigma and seeking HIV services.

Monitoring and evaluation systems to track outcomes and ensure accountability

Simplified, integrated monitoring and evaluation systems are necessary to ensure reliable drug supply, track input and programme effectiveness, and for programme accountability. Such systems need to be integrated within the existing health information systems and simplified for community health workers and people living with HIV themselves to complete them accurately and timely. Where possible, reporting requirements from community based services should be limited to the most vital and necessary, to minimize the workload that may discourage the involvement of care providers and people living with HIV.

Knowledge gaps and research priorities in community ART delivery

There are knowledge gaps and questions that need to be answered both in trials and from observational and implementation studies. First, across the literature and programmes, judgement differs regarding what defines a “stable patient” and how rigid such inclusion criteria should be applied for referral to community-based ART services. Also unknown is the proportion of people who meet these “stable patient” criteria. Of the nearly 10 million people receiving ART at the end of 2012, it is unknown what proportion have been on treatment for extended periods of time and could be managed with less frequent clinical contact; however, this is likely to be the majority.

Second, limited data exist on the preferences for community ART delivery systems and how these models of care enable patient empowerment and human rights. In addition to the need to document patient experiences, documenting processes and inputs needed for scaling up and implementing these models at the district, regional and national levels can support programme learning.

Third, there is considerable interest in how out-of-clinic community models can support underserved populations who often experience inequitable access to ART, including but not limited to men, children, adolescents, pregnant women, sex workers, men who have sex with men and people who inject drugs.

Fourth, data on the long-term effectiveness of these models in relation to patient outcomes are needed. Community models can offer benefits not just for the targeted stable ART population but also potentially for improving outcomes at different levels of the treatment cascade. Although evidence supports the provision of community-based HIV testing and ART maintenance, evidence is needed to assess the ranges of other HIV services that could safely be delivered at the community level.
Finally, more cost information is needed. Although community models are not primarily designed to save costs, it is important to determine what their costs are and their cost-effectiveness in different settings. In addition, understanding the resources needed to implement these models needs to be documented. This includes health workers’ time and workload analyses to further clarify resource requirements in different settings.

Continued innovation will be necessary to support the growing cohort of people living with HIV who are receiving ART. The current community models of care are an initial step of what and how services can potentially be provided closer to the homes of people living with HIV. Complementary to this innovation is the role of technology in supporting and engaging people living with HIV and communities.

Conclusion
There is no one-size-fits-all approach to community models of ART delivery. The context in which they operate is important, and models need to be flexible and responsive to the needs of people living with HIV. Community models are also designed to strengthen facility-based models by providing appropriate decentralized care, by minimizing congestion of health facilities and by allowing clinicians to see only the people who would benefit from clinical consultation. The needs of people living with HIV may vary over time, and links between community and facility models of care are necessary to ensure quality along the care pathway. Community models of ART delivery are not intended to replace existing services and very much need to operate as part of a continuum of care with facility-based care models. In addition, multiple community-based models might be implemented depending on local context.

The sustainability of community models of care is essential to ensure their long-term effectiveness. Although many models have been innovative and piloted by not-for-profit organizations, governments increasingly recognize that these models can be successfully implemented without huge external resources. Sustainability depends on appropriate support for the models of care, by incorporating such models in national programming and health care delivery systems.

ANNEX 11.1. Summary of examples of models of community ART delivery

<table>
<thead>
<tr>
<th>Model of care</th>
<th>Country, implementer and year</th>
<th>Criteria for delivering ART</th>
<th>ART refill interval</th>
<th>Frequency of clinic visit</th>
<th>Patient–provider ratio, human resources used and organization</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community adherence groups (14,15)</td>
<td>Mozambique Ministry of Health Lesotho, Malawi, South Africa and Zimbabwe (Médecins SansFrontières) 2011–present</td>
<td>Stable on ART Piloting inclusion of pre-ART people living with HIV</td>
<td>Monthly (Lesotho and Mozambique), every 2 months (Malawi), every 3 months (Zimbabwe)</td>
<td>Every 6 months (Lesotho, Malawi and Mozambique), annually (Zimbabwe)</td>
<td>Self-forming groups of 6–10 people living with HIV rotate to collect ART for the group. Groups formed with support from clinic staff and local networks of people living with HIV</td>
<td></td>
</tr>
<tr>
<td>Community adherence groups – pilot for the above (15)</td>
<td>Mozambique Médecins Sans Frontières 2008–present</td>
<td>&gt;6 months on ART, absence of adverse drug events, no opportunistic infection, CD4 &gt;200 cells/mm³</td>
<td>Monthly</td>
<td>Every 6 months</td>
<td>Self-forming groups of six people living with HIV rotate to attend the clinic and collect ART for the group</td>
<td>93.4% retention rate in care at 3 years and 91.8% at 4 years (16); children in community adherence groups reporting 94% retention (11) Uptake around 50%</td>
</tr>
<tr>
<td>Model of care</td>
<td>Country, implementer and year</td>
<td>Criteria for delivering ART</td>
<td>ART refill interval</td>
<td>Frequency of clinic visit</td>
<td>Patient–provider ratio, human resources used and organization</td>
<td>Remarks</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>---------------------------</td>
<td>----------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Adherence support (17,18)</td>
<td>South Africa Khet’impilo 2004–present</td>
<td>All people living with HIV</td>
<td>Not reported</td>
<td>Not reported</td>
<td>80–120 per community health worker All people living with HIV receive regular support in their homes from their community health worker</td>
<td>Lower rates of mortality and loss to follow-up, higher rate of viral suppression</td>
</tr>
<tr>
<td>Community drug distribution point</td>
<td>Uganda, TASO 2006–present</td>
<td>ART ≥10 weeks, defined as stable by clinician at the individual level</td>
<td>Every 2 months</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Reported 70% accessing ART</td>
</tr>
<tr>
<td>Community-based accompagnement for ART</td>
<td>Rwanda Partners in Health 2005–2006</td>
<td>All people living with HIV at ART initiation</td>
<td>Daily, directly observed therapy by community workers</td>
<td>Every 6 months</td>
<td>6 people living with HIV per community health worker</td>
<td>92% retention in care after 24 months Currently exploring approaches to reduce the frequency of home visits Expansion to &gt;20 000 people living with HIV over 18 months, and one fifth are now managed in a club 10–40% of the people living with HIV in each facility are accessing ART using this model</td>
</tr>
<tr>
<td>Adherence clubs – expansion</td>
<td>South Africa Provincial department of health and partners 2011–present</td>
<td>≥18 years, ART ≥12 months, two consecutive suppressed viral loads, no clinical condition requiring more frequent clinical consultation</td>
<td>Every 2 months</td>
<td>Annually</td>
<td>20–30 people living with HIV per club Number of clubs and community health workers not reported In the community, clubs meet outside the health facility in community venues</td>
<td>10 home-based clubs to date</td>
</tr>
<tr>
<td>Community ART distribution</td>
<td>Democratic Republic of the Congo Médecins Sans Frontières 2010–present</td>
<td>Receiving ART for &gt;6 months, absence of opportunistic infections, CD4 &gt;350 cells/mm³</td>
<td>Every 3 months</td>
<td>Annually</td>
<td>Not reported People living with HIV provide refills, adherence support and follow-up</td>
<td>Retention 89% at 12-month follow-up 43% of patients accessing ART in this model Reduced personnel cost and reduced transport and time cost for people living with HIV (11).</td>
</tr>
<tr>
<td>Adherence clubs – home-based expansion (9)</td>
<td>South Africa Médecins Sans Frontières 2012–present</td>
<td>≥18 years, ART ≥12 months, two consecutive suppressed viral loads, no clinical condition requiring more frequent clinical consultation</td>
<td>Every 2 months</td>
<td>Annually</td>
<td>10–15 people living with HIV per adherence club that meet in people’s homes</td>
<td>10 home-based clubs to date</td>
</tr>
</tbody>
</table>