The needs for HIV treatment and care of children, adolescents, pregnant women and older people in low-income and middle-income countries

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\textbf{Objective:} Success in diagnosing and treating HIV-infected adults has, where HIV care and treatment is available, turned HIV into a chronic, rather than life-limiting disease. Progress meeting the needs of HIV-infected children, perinatally and horizontally infected adolescents, pregnant women and older people has lagged behind. We review the special needs and barriers to scaling up care and antiretroviral therapy (ART) coverage in these populations.

\textbf{Design and methods:} A literature review combined with personal views and operational experience specifically from countries covered by the Evidence for Action programme.

\textbf{Results:} Challenges include logistics of diagnosis and treatment in pregnancy, difficulties in early infant diagnosis, availability of appropriate paediatric formulations, management of adolescents, and comorbidities in older people.

\textbf{Conclusion:} Priorities for development need to focus upon the simplification of HIV care to allow provision for all ages at the primary healthcare level. Specific priorities include focused use of virological testing in infants, ongoing development of dispersible and scored fixed-dose ART combinations suitable for use across ages, development of ‘adolescent-friendly’ HIV services catering for perinatally and horizontally infected adolescents to improve adherence and reduce onward transmissions, simplification of referral pathways to ensure all pregnant women are tested for HIV and commenced on ART, and education of healthcare workers on the specific needs of HIV care in older patients. Each priority will be reviewed and potential solutions discussed.

Keywords: adolescents, HIV, infant diagnosis, older people, paediatric HIV treatment, pregnant women

\textbf{Introduction}

An estimated 2.5 million children worldwide are infected with HIV; 90\% of them live in sub-Saharan Africa (SSA), where annually 330,000 new infections occur. Successful prevention of mother-to-child transmission (pMTCT) programmes can reduce transmission to less than 5\%, although coverage remains disappointing; in 2010 only, approximately 50\% of diagnosed HIV-infected pregnant women in low-income and middle-income countries (LMICs) received any antiretroviral (ARV) drugs for pMTCT [1]. In high HIV prevalence countries, child mortality rates have not followed the global decline in childhood mortality, mainly due to mortality associated
with untreated HIV, particularly in infants [2]. Advances in paediatric roll out of ART lag significantly behind adults; in 2010, 1.3 million children in LMICs were estimated to be in need of ART, but just 28% were receiving it, compared with 36% of the adults in need [1]. Intercountry variations in ART coverage are considerable (e.g. 2% in Sudan vs. >90% in Botswana) [3]. Without treatment, approximately 50% HIV-infected children die by 2 years of age [4]. When ART is available, children have a high chance of surviving into adult life, bringing new management challenges, particularly during adolescence. Adults on ART are now surviving into their 60s and beyond, meaning HIV must be managed as a chronic disease with other co-morbidities. The emphasis of HIV care must shift towards flexible, sustainable, decentralized and family-centred services, offered at primary health facilities from ‘cradle to grave’.

In the initial phases of ART scale up, the specific needs of children, perinatally infected adolescents and elderly were neglected compared with horizontally infected adults aged 15–59 years. Treatment 2.0, an initiative launched by UNAIDS and WHO to increase efficiency, effectiveness and harmonization of HIV treatment across all groups, aims to move towards universal ART access [5]. In particular, strategies for pMTCT have the potential to nearly eliminate new paediatric infections [6,7]. A global plan ‘Countdown to Zero’ (UNAIDS/PEPFAR) was launched in June 2011 with commitment to eliminating new paediatric HIV infections and ensuring that all women, especially pregnant women, have access to HIV prevention and treatment services by 2015 [8].

Methods

This paper reviews progress made in ART rollout to these specific groups highlighting future challenges and gaps in knowledge with some potential solutions discussed. A literature review was undertaken and combined with personal views and operational experience specifically taken from countries covered by the Evidence for Action programme. Evidence for Action was a 5-year international research programme that focused on HIV treatment and care systems working with partners in the UK, Uganda, Malawi, Zambia and India [9].

Paediatric HIV infection

The successes of ART in HIV-infected adults are equally applicable to children, if comprehensive paediatric HIV care is available. Despite rapid disease progression without ART, if diagnosed early, children respond well to ART, likely related to the ability of the young immune system to reconstitute. Infant mortality on ART has been reported to be similar to that in uninfected infants [10]. Survival of vertically HIV-infected children into adolescence and beyond (where ART is available) is well demonstrated in high-income countries (HICs) [11] and some LMICs [12]. The effects of HIV and ART on ultimate growth, neurological development, psychological well being, educational attainment and quality of life need further research as children move through adolescence into adulthood. ART strategies must recognize the difficulties of ART adherence during adolescence when young people are often struggling to understand their own and family members’ HIV diagnoses [13]. Adolescent care requires innovative ways to engage young people, particularly through peer support [14]. Ensuring vertically HIV-infected children reach adulthood with treatment options ahead of them and minimal toxicity from ART requires further research spanning adult and paediatric care.

HIV-infected children’s needs vary across childhood; increasing drug doses, different formulations and varying degrees of supervision taking ART. Issues such as the timing of HIV disclosure must be tackled within the context of their family and environment. In addition, particularly if children have already lost one or both parents, changes in caregiver and moving home (e.g. if the caregiver dies) further complicate follow-up and adherence. Several African programmes have reported high loss to follow-up among HIV-infected children receiving ART; it is often unclear what proportion has died, is no longer receiving care or ART, or is receiving ART from other providers [15–17].

Concrete major barriers to paediatric ART scale up in LMICs have been identified: difficulties in early infant diagnosis, developing alternatives to liquid formulations and shortage of healthcare personnel experienced in treating HIV-infected children. However, many aspects of paediatric treatment are similar to adults and, provided children’s needs are recognised, there are many benefits to treating adults and children together at health centres close to where families live.

Diagnosis of HIV infection in infancy

Rapid diagnosis of HIV is essential to reduce the high mortality in early infancy. Standard antibody tests cannot diagnose HIV before 10–18 months, as placentally transferred maternal HIV antibodies are indistinguishable from those of an infected infant. The gold standard for infant HIV diagnosis is one of three virological tests: HIV DNA on whole blood or dried blood spots (DBSs), HIV RNA on plasma or DBSs or ultrasensitive p24 antigen on plasma [18]. These have specificities and sensitivities of over 99% when used from 6 weeks of age [19–22]. However, equipped laboratories remain limited and
centralized. Although technology to extract and measure nucleic acids (DNA or RNA) from DBS, not requiring refrigeration, has helped to widen coverage [23], the logistics remain a challenge. Median delays of 6 weeks between testing and returning results are common, leading to high levels of loss to follow-up and disease progression; in 2010, only 6% HIV-exposed infants living in LMICs received virological testing results by age of 2 months [1]. Nevertheless, use of mobile phone SMS technologies to relay results are being explored and have shown promise in some LMICs [24,25]. The financial costs and logistics of infant diagnosis have so far prevented significant scale up of virological testing of all at-risk infants. Many programmes have focused on testing infants born to mothers in pMTCT programmes, wherein the HIV pickup rate is obviously encouragingly low, rather than prioritize limited resources to populations that have a greater rate of undiagnosed infection. Although clinical algorithms have relatively low sensitivity for identifying HIV among exposed infants [26], they should be pursued to help identify those requiring virological testing [27]. There is also need to increase access points for testing infants whose mothers are unaware of their own diagnosis – both in hospitals (e.g. malnutrition wards wherein 30–50% of children may be infected [28,29]) and community (e.g. immunization clinics). Although policies to screen (for HIV antibody) all infants and children admitted to hospital have been developed, implementation is patchy and hampered by shortage of testing kits [30].

Early results from the CHER trial showed that ART commenced early in infancy reduced mortality and morbidity [10]. This strategy was rapidly adopted by WHO ART guidelines (Table 1) [31–33]. However, there remains a mismatch between testing and starting ART; in 2009, less than one third of children tested and in need of treatment were given ART, reflecting delays in feeding results back, loss to follow-up and rapid disease progression, and lack of access to paediatric ART services especially in rural areas [34]. Although the progress in early infant diagnosis is encouraging, this must be matched by increased paediatric ART provision.

| Table 1. WHO 2010 guidelines – when to start antiretroviral therapy. |
|---------------------------|-----------------|-----------------|
| Age                       | When to start ART       | Comments                                                                 |
| Infants and children <2 years of age | Start ART immediately upon diagnosis | Evidence to treat under 1 year of age from CHER trial and European Infant cohort [10,32]. Decision to treat all under 2 years of age made to simplify ART initiation at an age when symptoms or CD4 tests are poorer predictors of disease progression than in older children |
| Children ≥2 years and <5 years of age | ≤25% CD4 or CD4 cell count of ≤750 cells/µL or clinical stage 3/4 | After 4–5 years of age, the absolute CD4 cell count predicts disease progression similarly to that in adults [33] and guidance is hence the same as in adults |
| Children ≥5 years of age | CD4 cell count of ≤350 cells/µL or clinical stage 3/4 |                                                                 |

ART, antiretroviral therapy. Data from [31].
Which antiretroviral therapy to start?

Optimal paediatric first-line ART is a balance between affordability, availability, toxicity and sustainability. Annual costs of first-line therapy have reduced dramatically with production of generic drugs [US$ 50–100 in 2009 compared with ~US$ 10 000 a few years earlier] [34]. WHO guidelines for first-line ART in 2010 are summarized in Table 2. The 4-year multicentre European and American PENPACT-1 trial concluded that both nonnucleoside reverse transcriptase inhibitor (NNRTI) and the more expensive protease inhibitor based first-line regimens had similar long-term efficacy [49], although the number of children less than 3 years of age was limited. Results from the IMPACT 1060 largely sub-Saharan African trial suggested that in children less than 3 years of age with perinatal NVP exposure, a boosted protease inhibitor [lopinavir/ritonavir (LPV/r)] was superior to NVP; this superiority extended to young children not exposed to NVP [50,51]. For young children, a more potent regimen, less fragile to development of resistance, would be preferable. In view of the difficulties and cost of LPV/r syrup, alternative approaches are to start with a protease inhibitor regimen in infants and then simplify to a NVP regimen [52,53] or to start with a four-drug, two-class (NNRTI + three NRTIs) regimen, which has been shown to be superior immunologically and virologically in European infants [32]. Results of long-term efficacy with a four-drug induction–maintenance approach in African children are awaited from the ARROW trial. The development of new paediatric HIV drugs, particularly for the very young child, lags behind adults; the Drugs for Neglected Diseases initiative organization recently announced plans to develop appropriate drugs for young children [54]; some potential new ARVs for paediatric use are listed in Table 3.

Optimizing paediatric fixed-dose combination formulations

Triomune baby and junior, a FDC of d4T/3TC/NVP with a higher ratio of NVP compared with adult formulations, was shown to have appropriate pharmacokinetics, good efficacy and tolerability in the CHAPAS 1 trial [55], resulting in FDA approval in 2007. Through the Clinton HIV/AIDS Initiative, in conjunction with UNITAID, this FDC has been distributed across 26 nations and remains effective and highly affordable for many thousands of children in LMICs [56]. Stavudine (d4T) is potent, can be taken without food restrictions, requires minimal laboratory monitoring and has few short-term side-effects, particularly in young children. However, long-term changes in fat distribution (lipodystrophy and lipoatrophy) have been clearly documented, particularly in peri/postpubertal women, those with higher CD4 cell counts and adults with a BMI of over 25 kg/m² [57]. Following these concerns, WHO 2010 guidelines recommended phasing out d4T, recommending its use in children starting ART to be restricted to situations where ZDV or ABC is not available or not tolerated. The major restriction for ABC is cost, as hypersensitivity reactions in Africans are rare [58]. d4T toxicity appears to be infrequent in young children, but no studies have compared its toxicity with that of ZDV, particularly in countries with high prevalence of malaria and anaemia wherein the risk of ZDV-induced anaemia is unequal breaking of unscored tablets can be problematic and, for some drugs especially nevirapine (NVP), can result in underdosing in young children who required a higher dose of NVP compared with other drugs [46]. The development of WHO weight–band tables (Annex E of WHO 2006 and 2010 guidelines) for paediatric scoring, solid FDCs, harmonized across drugs has greatly simplified drug prescribing. Adult, preferably scored, single-drug formulations and FDCs remain an effective option for older children, backed up by pharmacokinetic studies based on WHO weight–band prescribing [47]. Studies have also shown that carers and children prefer tablets to syrups [48]. In future, to simplify further, FDCs for both adults and children could be harmonized by appropriate scoring of the tablets to facilitate programmatic management, secure drug production and reduce costs.

Table 2. Summary of WHO recommended first-line antiretroviral therapy regimens for infants, children and adolescents.

<table>
<thead>
<tr>
<th>For children not exposed to maternal or infant nevirapine or whose exposure status is unknown</th>
<th>For children exposed to maternal or infant nevirapine or other NRTIs used for maternal treatment or pMTCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen of 2 NRTIs + 1 NNRTI</strong></td>
<td><strong>Regimen of 2 NRTIs + PI</strong></td>
</tr>
<tr>
<td>ZDV + 3TC + NVP/EFT</td>
<td>ZDV + 3TC + LPV/r &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ABC + 3TC + NVP/EFT &lt;sup&gt;a&lt;/sup&gt;</td>
<td>ABC + 3TC + LPV/r &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>d4T + 3TC + NVP/EFT &lt;sup&gt;a&lt;/sup&gt;</td>
<td>d4T + 3TC + LPV/r &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

If receiving TB treatment, EFV is the preferred over NNRTI in children older than 3 years of age. For children under 3 years of age who need TB treatment, nevirapine + two NRTIs or abacavir + lamivudine + zidovudine/stavudine is given. For adolescents co-infected with hepatitis B, TDF + FTC or 3TC + NNRTI is given. A preferential order of NRTIs (zidovudine/lamivudine > abacavir/lamivudine > stavudine/lamivudine) to be decided at a country level is suggested. ABC, abacavir; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; pMTCT, prevention of mother-to-child transmission; 3TC, lamivudine; TB, tuberculosis; TDF, tenofovir; ZDV, zidovudine. Data from [31].

<sup>a</sup>EFV for 3 years and older.

<sup>b</sup>If available, if not NVP should be given.
of greater concern. Lipodystrophy appears to be considerably less frequent in prepubertal children [59]. For these reasons, it may be premature to move away from d4T-containing regimens in young children until further toxicity studies are completed. ZDV-based paediatric triple-drug FDCs and ABC-based dual (with 3TC) FDCs are available and the latter can be administered once daily. Of note, the cost of ZDV-containing and ABC-containing FDCs is twice and thrice that of d4T. The ongoing CHAPAS 3 trial (ISRCTN69078957) compares the toxicity/efficacy of FDC mini-tablets containing ABC or ZDV or d4T. This trial should also inform about the age at which children on d4T should be moved to minimize toxicity.

Treatment 2.0 is committed to increasing harmonization across adult and paediatric guidelines, including exploring ways to ensure sustainable supply of drugs for children as ART provision is decentralized. Given the small market for paediatric drugs, FDCs suitable for use in both adults and children should be prioritized. This is unlikely in young children, as differences in the relative ratios of individual ARV drugs within the FDC and many of the potential candidates for new FDCs are not licensed in infants. The FDA, but not EMA, approved the use of tenofovir for children aged 2 years or above in January 2012, providing the possibility of a once daily FDC for older children and adults. A 600-mg EFV tablet scored to provide 200, 300, 400, 500 and 600 mg doses from age 3 years is being studied in the CHAPAS 3 trial (ISRCTN69078957). Other studies on drug/formulation optimization and strategies are summarized in Table 4.

### Duration of treatment in children – once started is antiretroviral therapy for life?

Children on ART are exposed to both HIV and ART throughout childhood. Strategies to limit potential for drug toxicity while ensuring optimum clinical well being (including growth and psychosocial/ neurological development) are being explored for children. Challenges of sustained adherence, potential for inadequate drug dosing [60] and lower viral suppression rates [61] all increase the risks of children acquiring multidrug-resistant HIV before reaching adulthood [62]. Potential strategies include interruption following early treatment in infants (CHER

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV</td>
<td>PI</td>
<td>A preferred PI in adults; is administered once daily and the least costly PI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approved for 6–18-year-olds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Needs to be boosted with ritonavir 🃏</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Could be used as an alternative to LPV/r in infants exposed to perinatal NVP. There is a need for paediatric formulations (co-formulated with ritonavir at a fixed ratio – preferably the same as adults)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More data needed on use in children under 6 years of age</td>
</tr>
<tr>
<td></td>
<td>Approved for 6–18-year-olds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A paediatric tablet (75 mg) is available and there is a potential to develop a FDC with ritonavir (and possibly with other ARVs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Needs to be boosted with ritonavir 🃏 and appropriate ratio of DRV : ritonavir for FDC (preferably the same as in adults)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be used following failure of LPV/r, and thus as second-line following LPV/r use in infants exposed to perinatal NVP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Once daily dosing is possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>There is a need for paediatric formulations and PK/safety studies in children less than 6 years of age</td>
<td></td>
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<tr>
<td>RAL</td>
<td>Integrase inhibitor</td>
<td>Potential third-line treatment in adults</td>
</tr>
<tr>
<td></td>
<td>Excellent chewable paediatric formulation for children</td>
<td></td>
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<tr>
<td></td>
<td>Ongoing paediatric studies from 4 weeks of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Needs to be given twice daily</td>
<td></td>
</tr>
<tr>
<td>ETV</td>
<td>NNRTI</td>
<td>Potential as third-line therapy in adults</td>
</tr>
<tr>
<td></td>
<td>Not currently approved for paediatric use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good potential drug to follow NVP exposure in utero</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paediatric trials ongoing down to 3 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generally well tolerated with good toxicity profile</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>NNRTI</td>
<td>Cheap to produce (US$ 10 per patient per year)</td>
</tr>
<tr>
<td></td>
<td>Potential to use in long-acting formulations (injectable nanosuspension being developed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Need to study safety and efficacy of higher doses in adults and appropriate doses in children; ongoing studies so far only in children older than 12 years of age</td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Integrase inhibitor</td>
<td>Very potent at low doses, so lower production costs</td>
</tr>
<tr>
<td>S/GSK1265744</td>
<td>Integrase inhibitor</td>
<td>Paediatric dose-finding study ongoing with a paediatric formulation</td>
</tr>
</tbody>
</table>

*ARV, antiretroviral; ATV, atazanavir; DRV, darunavir; ETV, etravirine; FDC, fixed-dose combination; LPV/r, lopinavir/ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PK, pharmacokinetic; RAL, raltegravir. *But ritonavir syrup is very bitter and contains 43% alcohol.
Perinatally infected adolescents

Adolescence (defined by WHO as age 10–19 years) is a period of rapid physiological, social and behavioural changes; sexual maturation occurs alongside increasing independence and evolving legal capacity. As numbers of perinatally infected adolescents increase with ART coverage [73], psychosocial support (particularly around HIV disclosure), access to reproductive health information and appropriate adherence support are vital, as adolescents frequently face barriers in accessing adult services and paediatric services are no longer appropriate. Disclosure is not a discrete event, but a process starting at a young age and completed ideally by early adolescence with appropriate psychological support provided throughout [74–76]. Whether the young persons are told their diagnosis by family members or medical professionals varies with individual circumstances. Lack of awareness that vertically acquired HIV may present during adolescence may result in late diagnosis; a study of hospitalized adolescents in Harare found a high burden of opportunistic infections associated with HIV-uninfected adolescents [12,77]. Ugandan data have revealed high levels of stunted growth and pubertal delay which responds only partially to ART [78,79]. Several studies have highlighted the need for ongoing sexual and reproductive health education for HIV-infected adolescents which is ‘adolescent-friendly’ to limit onwards transmission; for example, only one third of Ugandan adolescents were found to use condoms at sexual debut, and this was mainly for contraception rather than prevention of HIV/STDs [80]. Psychological support for vertically infected adolescents needs to appreciate visible effects of HIV: the impact of stunted growth, delayed puberty and dermatological manifestations upon young peoples’ self-esteem and a family focus to address parental issues around guilt or fear of disclosure in addition to the adolescents needs.

Horizontally HIV-infected adolescents

Delays in diagnosing horizontally HIV-infected youth are reported – infection is often asymptomatic, they may be
unaware of their risk of infection or not tested due to a lack of recognition from care providers that an adolescent has had their sexual debut. Girls are at greater risk of contracting HIV; a result of greater physiological susceptibility and a less control over sexual situations and condom use. Sexual and reproductive health education starting early in adolescence (10–14 years) is imperative to curbing the spread of HIV; by late adolescence [15–19], the risk of infection for young people in high-prevalence countries is already considerable. Routine and targeted testing, whether integrated into existing clinic services or outreach based in for example schools must be expanded. Once diagnosed, horizontally infected adolescents have traditionally been treated within adult services; however, adherence and virological outcomes are poorer in this age group compared with their adult counterparts. Accepting this turbulent period, adolescents appreciate dedicated clinics with age-appropriate activities run by knowledgeable, nonjudgmental and welcoming professionals trained in adolescent care. Offering integrated services (e.g. regular healthcare, ART, condoms and family planning) further reduce barriers to accessing care [81].

Management of pregnant women

High rates of unplanned pregnancy in HIV-infected African women have been reported even with regular medical review, contraception education and free contraception [82]. Diagnosing HIV-infected pregnant women and engaging them in pMTCT programmes early in pregnancy is essential for optimal maternal health while minimizing onwards transmission. Universal HIV testing of pregnant women is having success in some countries such as Botswana and South Africa. However, in 2009, only an estimated 26% of the 125 million pregnant women in LMICs received an HIV test [83], despite reports of high acceptance rates in the antenatal setting – for example, in Zambia and Uganda [84,85].

Although HIV testing is the first critical step in pMTCT programmes, it is only the first of several steps required to maximize women’s health and reduction in perinatal transmission. HIV-positive pregnant women then need to be assessed for lifelong ART, start ART if required and followed up. After diagnosis, many women do not receive HIV treatment and care services [82]. Qualitative research in Kenya and Tanzania has identified missed opportunities including complex patient pathways, lack of coordination between ANC and HIV treatment clinics, poor quality of care, personal reasons (e.g. cost of transportation, denial, competing priorities) and societal factors such as stigma [86]. There is a need for ‘joined up’ services to ensure that diagnosed HIV-infected women do not miss opportunities to receive ARVs for pMTCT or lifelong HAART for themselves. Engaging male partners in ANC care is important; women who do not disclose their HIV status to their partners are less likely to complete pMTCT programmes. In 2009, only half of the diagnosed HIV-infected pregnant women in LMICs received ARVs for pMTCT and ARV coverage for pMTCT was under 10% in many countries, including Nigeria with its large population [83]. Single-dose neviripine (sdNVP), to mother and baby, although efficacious and cheap, is no longer recommended as a third of mothers and half of babies infected will develop NVP resistance [87]. As reflected in WHO 2010 guidelines, whenever possible, women should receive a combination of ARV drugs to minimize MTCT as well as the risk of resistance (Tables 5 and 6) [88]. The key components of the updated guidelines are lifelong ART for pregnant women if needed for maternal health (WHO clinical stage 3 or 4 disease or CD4 cell count <350 cells/µl) starting as early as possible in pregnancy and ART prophylaxis during pregnancy, delivery and breastfeeding for women not currently needing to start ART for their own health. Two options (A and B) are available for pMTCT in the latter group of women with assumed similar efficacy but different cost implications [89,90]. National guidelines in approximately 65% African countries have opted for option A. Malawi, has decided to roll out a new option (option B+) in which all HIV-infected pregnant women are started on lifelong HAART immediately after diagnosis; this strategy obviates the need for CD4 testing before commencing ART (which is otherwise important to distinguish women needing ART for their own health from those in need of pMTCT only). As fertility rates are high (5.6 pregnancies per woman), this regimen offers protection for multiple pregnancies without the need to start and stop ART prophylaxis [6]. Evaluation of the success of this strategy will be eagerly awaited by the international community, but it is undoubtedly costly and other issues such as equity of access, adherence and development of resistance could have an impact. Continuous access to HIV healthcare during pregnancy and postpartum is vital, ideally fully integrated into antenatal care; currently, many pMTCT programmes have a high loss to follow-up [91].

Feeding infants born to infected mothers poses significant challenges due to the risk of HIV transmission via breastfeeding. Previously, avoidance or early cessation of breastfeeding was recommended; however, this resulted in high mortality rates due to diarrhoea, malnutrition and other diseases [92]. In the majority of LMICs, replacement feeding is not acceptable, feasible, affordable, sustainable or well tolerated. Without intervention,

| Table 5. Eligibility criteria for HAART or antiretroviral prophylaxis in HIV-infected pregnant women. |
| Maternal criteria | Recommendation |
| CD4 cell count ≤350 cells/µl or clinical stage 3/4 | Start HAART immediately |
| CD4 cell count >350 cells/µl or clinical stage 1/2 | Option A or B |

Options A and B are given in Table 6. Data from [7].
15–20% of breast-fed infants born to infected mothers will be postnatally infected [93–96]. Exclusive breast-feeding for the first 6 months is associated with a significantly lower risk of HIV transmission as compared with mixed feeding (breast milk and any other food or liquid including water) even in the absence of ART [89,96,97]. WHO guidelines (Table 6) recommend that maternal ART or neonatal NVP should be provided, depending on the pMTCT option adopted, until 1 week after all breastfeeding has ceased. With either of these strategies, postnatal transmission is reduced to 1–2% [98]. This underscores the need for improved antenatal HIV testing and pMTCT coverage, linkages with primary healthcare and ART services for continued care throughout pregnancy, delivery and breastfeeding.

With the expansion of pMTCT programmes, the population of HIV-exposed but uninfected children, exposed to ART in utero and during breastfeeding, is increasing. There are limited data on possible long-term outcomes in this group. Large cohort studies are required to follow this group to assess the impact on their later health and other outcomes [99].

### Diagnosis and access to services

Older people may have a delayed HIV diagnosis and delay in starting ART; they are also less likely to use HIV testing and counselling services (reduced awareness of the existence of services), due to increased stigma (especially women), poorer access or because they do not perceive themselves to be at risk of HIV [106,107]. In a 2005 national household survey in South Africa, 61% of people 50 years and above were aware of HIV services nearby, compared with over 80% at younger ages [108]. Overall, 18% had ever been tested for HIV, compared with 43% at 25–49 years of age. Medical workers may delay HIV testing in older people with AIDS, as they do not suspect HIV infection because of the similarity of symptoms of HIV infection or opportunistic diseases with other commoner conditions or signs of aging [109–111]. With increasing ART use, there will be more people over 50 years of age living with HIV infection, which may lead to increase incidence rates. Although ART reduces the risk of HIV transmission, it will be important to offer education about safe sex and HIV prevention to older people, as well as improve their access to prevention services.

### Older people

Population-based studies of HIV/AIDS among older people (50 years and older) are still rare. HIV infection rates are not negligible in LMICs [100]; in South Africa, HIV prevalence among men and women was 10.4 and 10.2%, respectively, at ages 50–54 years and 3.5 and 1.9%, respectively, at ages 60–64 years [101]. The significance of older people is likely to rapidly increase as a significant proportion of patients on ART are expected to live beyond their 50s and 60s [102–105].

### Treatment and care

Specific issues related to aging in HIV-infected people on ART include a poorer immune response to ART, the occurrence of frequent and more severe clinical complications, the existence of co-morbid conditions due to co-infections (e.g., hepatitis B or C) or risk factors (e.g. alcohol abuse, smoking) and the prevalence of co-morbid conditions associated with normal aging [104,106,112].
Most studies suggest older patients have a poorer immunological (although often better virological) response to HAART, although the evidence is not conclusive [111]. An important factor may be the delay in starting ART, so their nadir CD4 cell count is low, which is a major factor in increased mortality and immune response. The extent of side-effects of ART in older people is only beginning to be explored; increased liver and renal side-effects suggests that drug dosages should be adapted for older HIV-infected patients [106].

Co-morbidities such as cardiovascular disorders, cancer, chronic respiratory diseases, musculoskeletal diseases and diabetes are commoner among older people and will affect HIV treatment and care [106,113]. Studies have shown increased frailty, a measure of general weakness and mortality risk, in older HIV-infected patients, irrespective of ART status [114,115]. Few studies in LMICs have reported on the health status of HIV-infected older people on ART. Ugandan and South African studies showed that the health and functional status among HIV-infected older people on ART was nearly as good as HIV-uninfected older people [116,117]. To deal with co-morbidities and increased side-effects, integrated approaches to healthcare are essential; however, most LMICs have invested only piecemeal in developing appropriate health services for older people.

Adherence rates need special attention [111,118,119]. Older people are at greater risk of nonadherence because of lower levels of education than younger adults, competing family obligations, concurrent mental health problems (e.g. dementia, depression) and weaker financial position, especially of widows, but evidence is limited [120]. Stigma may play a role, especially for women who often are expected to uphold the moral traditions of their societies; communities view HIV status as evidence of women failing to uphold that moral imperative [121].

In summary, ART and care for infants, children, adolescents and older people lags behind that of adults (20–59 years), presenting unique challenges in HIV diagnosis, provision of ART and ongoing care. Although huge progress has been made, increasing coverage for all these specific populations is a large challenge for the future. Early identification of pregnant women so that they receive ART and care for themselves and pMTCT is a major focus for the worldwide community which will require concerted mobilization and political action. Older people are an important population with specific challenges related to co-morbid chronic conditions and ageing. All these populations need prioritization, particularly as to how to increase ART coverage and care in programmes in LMICs. Currently, although many ART programmes collate data by age groups when reporting on the health of the treated population, no paediatric-specific, adolescent-specific or elderly-specific ART programme monitoring indicators exist [122]. The appropriateness of using existing ART programme monitoring systems for these specific groups needs further evaluation.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

Predictors for mortality and loss to follow-up

Treatment of AIDS:


Mwaungulu FBI, Floyd S, Crampin AC, Kasimba S, Malema S, Kanyongoloka H, et al. Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculo-


adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi. AIDS 2003; 17:1033.

Wiktör SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, et al. Efficacy of trimethoprim-sulfamethoxa-


pressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART


National AIDS Commission MoHaP. Treatment of AIDS: guidelines for the use of antiretroviral therapy in Malawi. 1st


O’Brien DP, Sauvegoat D, Zachariah R, Humblet P. In re-


Nahiry-Ntege P, Bakura Dangarembizizi M, Cook A, Akeera-


The PENPACT-1 (PENTA 9 /PACTG 390) Study Team. First-line antiretroviral therapy initiation with a protease inhibitor versus nonnucleoside reverse transcriptase inhibitor combina-


89. WHO. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. 2009.