



MODULE 4: COINFECTIONS

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1. INTRODUCTION

Much of the morbidity and mortality caused by HIV infection is related to immunosuppression from poorly controlled HIV infection and subsequent disease from opportunistic coinfections. Coinfections usually require their own treatment, which may have implications for the antiretroviral therapy (ART) regimen because

of the potential for combined toxicity and drug–drug interactions. Proactively considering what key coinfections and their treatment imply for developing antiretroviral (ARV) drugs for children is therefore prudent. Coinfections of particular interest include tuberculosis (TB), hepatitis B virus (HBV) and hepatitis C virus (HCV).

2. COINFECTION WITH TB AND HIV

The global burden from TB, a disease caused by *Mycobacterium tuberculosis*, is enormous, with an estimated 10.4 million incident cases worldwide resulting in 1.4 million deaths in 2015, making it the single most deadly infectious disease globally (1). The burden of TB among children has been underestimated historically, but more recent attempts have revised the estimated number of incident TB cases among children substantially upward. As many as 1 million children are estimated to develop TB globally each year (1).

Case-fatality rates of untreated TB are as high as 44% among HIV-uninfected children older than 5 years and are significantly higher among children living with HIV, even when appropriately treated for TB (2). An estimated 210 000–240 000 children died from TB in 2015, making TB one of the top 10 causes of child mortality (2). Notably, the children most at risk for poor outcomes from TB, infants and other young children, are also the group for whom predicting drug–drug interactions is most difficult and for whom child-friendly formulations are the most important.

There are several important reasons to specifically consider TB coinfection in developing ARV drugs and formulations for children. First

is the substantial epidemiological overlap of TB and HIV in many settings. There are many reasons for this overlap, including at least in part the increased risk people living with HIV have of developing TB. The highest burden of childhood TB remains in sub-Saharan Africa and South-East Asia, where most children with HIV live, so coinfection is likely in many settings (2).

Even in settings with a low TB burden, children with HIV have a much higher risk of developing TB (3). Although ART reduces this risk substantially, people living with HIV receiving ART remain at increased risk of developing TB compared with children without HIV.

Second, TB remains one of the most important causes of mortality among children living with HIV worldwide. HIV infection potentially complicates the diagnosis of TB among children and increases the risk of morbidity and mortality. Efforts to reduce mortality among children living with HIV must therefore necessarily consider TB and work to ensure the optimal co-treatment of both infections.

Third, co-treatment of TB with ARV drugs introduces the potential for additive adverse effects. The recommended first-line treatment

regimen for drug-susceptible TB is a two-month intensive phase with rifampicin, isoniazid and pyrazinamide with or without ethambutol followed by a four-month continuation phase of isoniazid and rifampicin (4). Although children generally tolerate these TB medications well, they may cause hepatotoxicity, rash and other adverse effects, which overlap with the adverse effects of many ARV drugs.

Finally, and critically important for drug development, is the potential for drug–drug interactions (5). Rifampicin, a key TB drug uniquely capable of sterilizing TB lesions, shortening treatment and preventing relapse, is also a potent inducer of cytochrome p450 enzymes and important transporter proteins (5–8). These rifampicin-induced interactions may result in drastically reduced exposure of some ARV drugs, potentially jeopardizing their efficacy and also increasing risk for acquiring ARV drug resistance (5,9).

ARV drugs without clinically significant interactions with rifampicin would be ideal agents, but this is not possible for many ARV drugs currently in use and in development. Rifabutin, an alternative rifamycin to rifampicin, does not affect concentrations of protease inhibitors. However, protease inhibitors potently inhibit rifabutin's metabolism, and a small study of co-treatment among children was stopped early because of neutropaenia (10); this interaction and the safety of co-treatment with rifabutin and protease inhibitors needs to be studied further. In the absence of studies addressing the use of ARV drugs among children with TB, this important subpopulation may be receiving suboptimal ART; early inclusion of children with TB and HIV coinfection in studies of emerging ARV drugs is thus vitally important.

Because of the epidemiological overlap and importance of TB as a cause of morbidity and mortality among children living with HIV, the development of ARV drugs for children must ensure that co-treatment with TB is safe and effective.

2.1 Key challenges

The key consideration in developing ARV drugs for children from the perspective of TB and HIV co-treatment is to establish whether the ARV drug of interest and TB medication, primarily rifampicin, have drug–drug interactions. If drug–drug interactions are present, then the extent of the interaction should be characterized for children. For clinically significant interactions, alternative dosing should be established and formulations developed that will maintain target exposures of the ARV drug. Safety of the ARV drug, at the proposed dose to be used for co-treatment, must also be established for children co-treated for TB and HIV.

To establish these objectives, studies are needed among children, such as Phase I and II trials. Data from adults establishing the presence and degree of expected drug–drug interactions are highly informative for studies of children. However, drug–drug interactions may differ among children because of differences in developmental pharmacokinetics or formulations.

An important example is lopinavir/ritonavir (LPV/r), the key component of ART for children younger than three years. In contrast to adults, children given doubled doses of LPV/r combined with rifampicin-based TB treatment do not achieve adequate LPV exposure. This appears to result from differences in absorption among young children and is potentially related to the formulation for children (11,12). This highlights the need to study drug–drug interactions among children when developing formulations for children. Although adding additional ritonavir (super-boosting LPV to a 1:1 ratio of LPV/r) supports adequate LPV concentrations for children (13), lack of a suitable ritonavir formulation limits the adoption of this approach. Studies are therefore needed among children living with HIV, but these studies face several critical challenges.

2.1.1 Delays in initiating studies involving children

There are substantial delays in studying ARV drugs more generally among children (14). TB is often an exclusion criterion in early-phase studies of ARV drugs involving children that aim to establish the dose and safety of these drugs among children. In some ways this is sensible, since drug–drug interactions with components of TB treatment and the additional safety concerns may be problematic for emerging ARV drugs. In fact, trials of ARV drugs among children with TB are often not done at all, or if they are, it is only after the safety and optimal dosing of a drug has been established among children living with HIV but not TB. This leads to very long delays until sufficient experience is accumulated. Since the field is moving rapidly and new and better drugs are constantly being developed, by the time studies of children are underway or completed, the data are less clinically relevant since other newer ARV drugs have already taken priority. There is little incentive to include children coinfecting with TB and HIV in early-phase trials, since manufacturers do not and are not required to seek market authorization for use in TB and HIV co-treatment.

2.1.2 Lack of appropriate formulations for children

The lack of appropriate formulations for children is a major barrier to studying drug–drug interactions between TB medications and ARV drugs. Suitable formulations are often not available early in the drug development process, when these studies should be undertaken. In addition, the presence or extent of drug–drug interaction may depend on the formulation itself: as described above, for LPV/r, double-dosing with rifampicin for adults results in adequate LPV concentrations, but the liquid formulation results in low exposure for children (11).

Even when appropriate ARV formulations are available, the altered dosing that may be required

to address the interaction may further complicate formulation issues. If the components of a fixed-dose combination tablet are differentially affected by the interaction, alternative single-drug formulations of one or more components may be required. An example is the need for super-boosting LPV/r with additional ritonavir when co-administered with rifampicin for children coinfecting with TB and HIV. Additional ritonavir is needed to increase the ratio of LPV/r from 4:1 to 1:1; however, the ritonavir formulation for children is a poorly palatable liquid requiring refrigeration, which has limited the uptake of this strategy in many low- and middle-income countries.

2.1.3 Challenges of recruiting children for studies

Recruiting children to high-quality studies of TB and HIV co-treatment is increasingly challenging, despite the continued significance of TB coinfection to morbidity and mortality among children living with HIV. As services for preventing the vertical transmission of HIV continue to reach more children in better functioning health systems, where generally the capacity for implementing the required studies of children is concentrated, fewer children acquire HIV. Children in these studies who do become infected with HIV and develop TB are often those who have complicated social situations and have slipped through the existing services, often for the same reasons that make them challenging participants to enrol and keep in trials. In health programmes with gaps in preventing vertical transmission and other health services, although more children acquire HIV and TB, the capacity to enrol them into studies is often compromised.

2.1.4 Developmental pharmacokinetics and other design considerations

The maturation of many physiological processes during the first few years of life has the potential to greatly affect the pharmacokinetics of

drugs, sometimes in ways that are difficult to predict (15,16). Not surprisingly then, drug–drug interactions may also vary by age. Pharmacogenomic differences may also influence the degree and direction of drug–drug interactions (17). To account for this large potential variability, sample sizes must therefore be large enough to characterize pharmacokinetics and establish optimal doses across ages.

Drug–drug interactions between the ARV drug of interest and other ARV drugs may also complicate study design. If the optimal dose of an ARV drug administered with TB drugs is unknown, then it cannot be considered a component of a fully active ART regimen. In this case, the ARV drug being studied may be added on to a fully active standard ART regimen. However, existing recommended regimens contain medications such as efavirenz (EFV) or LPV/r, which may also interact with the ARV drug of interest, complicating the characterization of interactions with TB treatment.

2.2 Proposed solutions

2.2.1 Start studies and develop formulations for children earlier

Delays in evaluating novel ARV drugs among children coinfecting with TB and HIV must be reduced. One approach is to enable children living with HIV who develop TB while participating in trials of novel ARV drugs to have pharmacokinetic sampling and short-term safety monitoring after starting antituberculosis treatment, rather than immediately going off the study (see section 2.3 on the Odyssey trial). Dosing of the ARV drug in such a study can be based on the drug–drug interaction studies of adults. This opportunistic approach may not be formally powered to characterize such drug interactions but may provide meaningful data in an efficient and timely way. The risk of such an approach depends on the degree of expected drug–drug interactions based on preclinical and adult studies.

Potential risks to the participants from this approach, such as insufficient viral suppression because of unexpected interactions resulting in low ARV drug exposure, require careful management. The risk would likely be low if the ARV drug of interest was only given for a short period after starting TB treatment to perform pharmacokinetic sampling; the time taken for the interaction to mature, because of induction of enzymes and transporters, would need to be considered. Other ARV drugs could be added to the regimen so that the drug of interest is not relied on for viral suppression. Interim pharmacokinetic analyses could inform dosing in these trials once they open, further reducing risk.

There are other opportunities to accelerate studies among children. Many ARV drug trials involving children use an age de-escalation strategy, starting with older children and with progressively younger children enrolled in a stepwise fashion as data on safety and optimal dosage emerge. In this case, a trial of the ARV drug for TB and HIV co-treatment could be developed in parallel to a main trial, with age cohorts opening once safety and the optimal dosage have been established among children living with HIV but not TB rather than waiting until the entire trial is completed before opening a trial among children coinfecting with TB and HIV.

Suitable formulations for children must be developed much sooner and must consider potential drug–drug interactions among children coinfecting with TB and HIV.

2.2.2 Facilitate more rapid recruitment for studies

Ensuring more rapid recruitment for studies of children coinfecting with TB and HIV requires continued support for trial and clinical research capacity in settings with a high burden of both diseases. Multicentre studies involving multiple study sites in countries with a high burden of TB and HIV coinfection may provide the best opportunity to recruit efficiently. Studies should be designed as pragmatically as possible without

sacrificing safety, to avoid making eligibility criteria so strict as to be a barrier to enrolment in the study.

2.2.3 Pool data

Although it has its limitations, pooling data from multiple trials or studies that collect pharmacokinetic and safety data for co-treated children on the ARV drug of interest may provide data more rapidly than a single large adequately powered trial. This would also make opportunistic collection of data in trials (see section 2.2.1) potentially more useful. A collaborative mechanism to facilitate such data sharing and pooling would be a useful advance.

2.2.4 Use pharmacometrics

Pharmacometric methods may be very useful in TB and HIV co-treatment. Models can be used to appropriately scale data from drug–drug interaction studies of adults to better estimate optimal doses for co-treatment among children. This approach is likely to provide reasonable

estimates down to two years of age. For children younger than two years, there is more uncertainty because of developmental changes in pharmacokinetics and formulation effects.

Physiologically based pharmacokinetic modelling is becoming increasingly sophisticated and may improve dosage estimation among children younger than two years. This approach is likely to make studies more efficient by reducing the frequency of dosage adjustments and also by requiring fewer participants and fewer sampling time points to meet the study objectives. This is critically important, given the challenges of recruiting to these studies. In addition, population pharmacokinetic modelling is a powerful tool for pooling data across studies and subpopulations.

2.2.5 Consider the data required to make recommendations about co-treatment

There are clearly challenges to generating the relevant data needed to inform treatment recommendations for infants and other



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children coinfecting with TB and HIV. Even when suboptimal data are available, health-care workers need guidance based on the best available evidence. A pragmatic approach to developing treatment recommendations is needed, in which generating the highest-quality data is encouraged but the practical challenges in implementing studies in this population are considered. For guideline drafting, such organizations as WHO should consider developing a consensus about the highest-priority data and minimum data required to make treatment recommendations. Clear communication of this to researchers and industry could inform choices about how to most efficiently use resources and recruit children coinfecting with TB and HIV into research studies.

2.2.6 Collaboration and coordination between disease areas

Both TB and HIV therapeutics are rapidly developing. Changes in optimal medications, doses or formulations in either disease area have potentially important implications for children co-treated for TB and HIV. Improved communication between experts and drug developers in these areas will help anticipate potential challenges and develop timely and effective solutions. Focus on key ARV drugs that could be combined into 2–3 regimens for TB and HIV co-treatment, as identified by expert consensus and key organizations such as WHO, may help in setting priorities for limited resources.

2.3 Case studies

ODYSSEY trial

The ODYSSEY trial is a randomized controlled trial of dolutegravir (DTG)-based ART versus the standard of care (therapy based on protease inhibitors or non-nucleoside reverse-transcriptase inhibitors) among children living with HIV (ClinicalTrials.gov identifier NCT02259127). DTG is a new, highly potent

integrase inhibitor increasingly used as a key ARV drug among treatment-naïve and -experienced people living with HIV. It is metabolized by the UDPG1 and CYP3A4 enzyme systems, so drug–drug interactions are expected with rifampicin.

A Phase I drug–drug interaction study among healthy adult volunteers showed that 50 mg of DTG given twice daily along with rifampicin resulted in only slightly higher exposure than with the currently recommended 50-mg once-daily dose of DTG (18); however, questions remain about the optimal dolutegravir dose for TB and HIV co-treatment (19). Children who are treated with rifampicin for TB when entering the trial or who develop TB while in the trial will be eligible for a small TB pharmacokinetic substudy. While on rifampicin, these children will receive DTG twice daily (rather than once daily) and will have pharmacokinetic sampling for DTG while on rifampicin and then again when rifampicin has been stopped. This efficient approach uses the opportunity of having children coinfecting with TB and HIV in an already planned trial to generate critically needed data on DTG dosing in co-treated children. This practical solution should be replicated in other trials.

Pharmacokinetics of LPV/r superboosting among infants and other young children coinfecting with HIV and TB

This study, sponsored by the Drugs for Neglected Diseases initiative, was a multicentre, open-label, non-randomized, prospective, noninferiority study to compare the pharmacokinetics of LPV administered with superboosting (LPV/r 1:1) and concurrent rifampicin treatment or with standard boosting (LPV/r 4:1) without concurrent rifampicin treatment and to assess the safety, tolerance and viral effect of superboosting among infants and other children coinfecting with HIV and TB weighing >3 kg and ≤15 kg. Preliminary data from the study, completed in 2016, demonstrated non-inferiority for superboosting with concurrent rifampicin treatment and standard dosing without rifampicin regarding

trough LPV/r concentrations below target values. The trial identified several challenges and important lessons:

- Despite the pragmatic design, enrolment was slow, and strategies to improve study accrual are thus needed.
- Most children were ART naive.
- Treatment was failing for many children receiving ART, necessitating additional time and resources to be spent on supporting adherence and ensuring that there was no resistance.
- Better strategies are needed to assess adherence.
- Tolerability and acceptability should be assessed proactively (personal communication, Helena Rabie, Stellenbosch University, Cape Town, South Africa, September 2017) (see the module on pharmacokinetic modelling for additional information on this and related studies).

2.4 Future issues

Until recently, there has been little change to TB treatment, with no new TB drugs entering the treatment landscape. However, largely as a response to the problem of multidrug-resistant TB (defined as resistance to both isoniazid and rifampicin), this is changing. Repurposed medications, such as clofazimine and linezolid, are being introduced into multidrug-resistant treatment regimens. Further, two new medications for TB, bedaquiline and delamanid, have conditional approval for treating multidrug-resistant TB among adults. Bedaquiline, a diarylquinoline that inhibits mycobacterial ATP-synthase, is metabolized by CYP3A4, resulting in significant drug–drug interactions with EFV (estimated 52% reduction in bedaquiline concentrations) and LPV/r (three-fold increase in bedaquiline exposure) but not nevirapine (20,21).

Delamanid, a nitroimidazole compound that inhibits mycobacterial cell wall synthesis, is not expected to have significant interactions with ARV drugs, but it is partly metabolized

by CYP3A4. Its primary metabolite DM-6705, responsible for most of its QT-prolonging effect, is also metabolized by CYP3A4 (22). Potential drug–drug interactions and safety among children co-treated with ARV drugs and these medications must be characterized. The trials of bedaquiline involving children have been substantially delayed, opening only in 2016, and the trials of delamanid involving children completed enrolment at the end of 2017. However, neither trial included children living with HIV. Trials involving children with HIV are beginning to be set up through the IMPAACT (International Maternal Paediatric Adolescent AIDS Clinical Trials) Network, but this delay has important implications for children living with HIV, especially for bedaquiline, for which clinically significant drug–drug interactions are expected.

In addition, these and other new and repurposed medications have shown the potential in preclinical studies to shorten TB treatment (23–25), and there is thus much work ongoing to develop shorter regimens for drug-susceptible TB with combinations of these medications. These medications will therefore probably find a more prominent role in TB treatment, and ensuring that these medications can be used safely and effectively for children coinfecting with TB and HIV is even more crucial. Leaders in developing both TB and HIV drugs for children must be aware of the advances in both fields that have implications for likely future treatment regimens for both diseases.

2.5 Useful resources

Chapters 4 and 5. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en>, accessed 22 May 2018).

3. COINFECTION WITH HBV AND HIV

Chronic HBV infection affects 5–20% of the 36 million people living with HIV worldwide, and the burden of coinfection is highest in South-East Asia and sub-Saharan Africa (26). In countries with high endemicity (seroprevalence >8%), where implementation of birth and infant HBV vaccination has been suboptimal, vertical transmission remains the main route of HBV transmission for children, followed by horizontal transmission. Horizontal transmission includes from child to child, within the household and within the extended family as well as transmission through inoculation of minute amounts of blood or fluid during medical, surgical and dental procedures through poor injection safety and traditional practices (such as scarification or circumcision). In countries with low HBV endemicity and/or in which the prevention of vertical transmission through infant vaccination has been widely implemented, HBV infection is uncommon among children.

The 2016 WHO consolidated guidelines on the use of ARV drugs (27) recommend that children coinfecting with HIV and HBV be given priority for ART because of the increased risk of fibrosis progression, cirrhosis and hepatocellular carcinoma. WHO recommends that children with chronic hepatitis B and clinical evidence of cirrhosis be treated for HBV regardless of alanine aminotransferase levels, hepatitis B e antigen status or HBV DNA levels. Antiviral treatment options for children with HBV include interferon α , pegylated interferon- α -2a and the nucleoside and nucleotide analogues lamivudine, adefovir, entecavir and tenofovir (28).

3.1 Key challenges

No published studies on HBV treatment among children have included children coinfecting with HIV and HBV, and no antiviral drugs are labelled

for the treatment of children coinfecting with HIV and HBV.

The recommended first-line nucleoside reverse-transcriptase inhibitors tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) (or emtricitabine (FTC)) in adults and adolescents are active against HBV. Among children 3–9 years old, the first-line nucleoside reverse-transcriptase inhibitors are abacavir (ABC) + 3TC or TDF + 3TC. However, ABC + 3TC is preferred because TDF causes significant bone and renal toxicity. Further, TDF formulations for younger children are not widely available and, to date, there are no TDF-containing fixed-dose combinations for children. Nevertheless, children coinfecting with HIV and HBV should be treated with a TDF-based regimen, and if ARV drugs need to be replaced because of HIV drug resistance, TDF with 3TC or FTC should be continued together with the new ARV drugs.

Tenofovir alafenamide (TAF) has good efficacy among adults living with HIV, with much less bone and renal toxicity. Although limited data exist on HIV and HBV coinfection, the 2017 European guidelines on HBV infection (29) recommend a TAF-based ART regimen for adults coinfecting with HIV and HBV. TAF is currently available in the adult formulations of fixed-dose combinations for children and adolescents weighing over 35 kg.

3.2 Proposed solutions

Including adolescents in trials involving adults coinfecting with HIV and HBV

To speed up the availability of antiviral drugs for HBV, one solution could be including adolescents in trials involving adults coinfecting with HIV and HBV. Adolescents can usually take the same dose as adults, since the

pharmacokinetics are similar, and there is therefore no need to wait until trials for adults are completed before starting ones for adolescents.

Development of TAF for younger children

TAF is about to become one of the main nucleoside reverse-transcriptase inhibitors for children living with HIV and HBV in the United States and Europe. The development of TAF for children weighing less than 35 kg, with appropriate formulations and fixed-dose combinations for children, should be a priority. This would allow the optimal treatment of HBV among children coinfecting with HIV and HBV.

Development of TDF formulations for younger children

TDF formulations for younger children and TDF-containing fixed-dose combinations for children are needed. However, if the development of TAF for children is given priority, the development of TDF formulations for younger children and TDF-containing fixed-dose combinations for children will be less crucial.

3.3 Case studies

Trial of TAF for HBV among adolescents

A trial is ongoing on TAF among adolescents 12–17 years old monoinfected with HBV (ClinicalTrials.gov identifier NCT02932150).

TAF switch studies among adults

A trial is ongoing on the safety and efficacy of switching from TDF and/or other oral antiviral treatment to TAF among adults monoinfected with HBV (ClinicalTrials.gov identifier NCT03180619).

3.4 Useful resources

- Guidelines for the prevention, care and treatment of people with chronic hepatitis B infection. Geneva: World Health Organization; 2015 (<http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines-policy/en>, accessed 22 May 2018).
- European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67:370–98.
- Chapter 5. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en>, accessed 22 May 2018).

4. COINFECTION WITH HCV AND HIV

In 2016, HCV affected an estimated 5–15% of the 36 million people living with HIV, rising to 90% among people who inject drugs. Low- and middle-income countries have the highest burden of coinfection. HCV-related liver disease progresses more rapidly among people living with HIV. All adults coinfecting with HIV and HCV should therefore be considered for HCV treatment.

The decision to start ART among children and adolescents coinfecting with HCV should follow the same principles as in HIV monoinfection. Potential harmful effects of ARV drugs include their hepatotoxic effects. For most people coinfecting with HIV and HCV, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. In treating people coinfecting with HIV and HCV, considering the potential risk of drug–drug interactions between HIV and HCV treatment regimens is also very important. People receiving ongoing HIV treatment should have stable viral control of HIV infection before initiating HCV treatment.

Children coinfecting with HCV and HIV have a lower rate of spontaneous clearance of HCV, are more commonly HCV viraemic and have higher alanine aminotransferase values than HCV-monoinfected children (30,31). Treatment in the past with interferon-based treatment with ribavirin was very difficult for children because of side-effects such as depression as well as severe anaemia, thrombocytopaenia and neutropaenia. Further, those old regimens yielded low rates of success among children and even lower among children coinfecting with HCV and HIV (32).

The newer, all-oral direct-acting antiviral HCV regimens produce similar and very high rates of sustained viral response among adults regardless of HIV status. Thus, direct-acting antiviral HCV therapy has substantially simplified the treatment of people coinfecting with HIV and HCV. There

are fewer drug–drug interactions between direct-acting antiviral HCV regimens and ARV drugs, and sustained viral response rates with direct-acting antiviral HCV therapy among people living with HIV are higher than 95%, even for those with previous HCV treatment failure or advanced fibrosis. People coinfecting with HIV and HCV therefore no longer need to be considered a special, difficult-to-treat population.

4.1 Key challenges

The United States Food and Drug Administration and European Medicines Agency recently approved sofosbuvir + ledipasvir, which is indicated for the treatment of adolescents 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5 or 6 infections without cirrhosis or with compensated cirrhosis. The decision was mainly based on a Phase II, multicentre open-label study of 100 adolescents with chronic genotype 1 HCV infection treated for 12 weeks with the adult formulation of sofosbuvir ± ledipasvir (400/90 mg daily).

Sustained viral response was documented for 98% of participants: the regimen was safe and well tolerated, with no grade 3 or 4 adverse events reported. The combination of sofosbuvir + ribavirin at doses approved for adults (400 mg and 15 mg/kg in two divided doses daily) was tested among adolescents with chronic HCV genotype 2, receiving 12 weeks of treatment, or genotype 3, receiving 24 weeks of treatment. Sustained viral response rates were 100% (13 of 13) and 97% (38 of 39) in genotype 2 and 3 infections, respectively.

This regimen was safe and well tolerated, and the pharmacokinetic properties of sofosbuvir were equivalent to those among adults. The United States Food and Drug Administration and European Medicines Agency therefore approved

sofosbuvir for adolescents 12 years of age and older or weighing at least 35 kg with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin, including adolescents coinfecting with HIV and HCV.

At this point, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines recommend that treatment of children 3–11 years old with chronic hepatitis C be deferred until interferon-free regimens are available (33,34).

Sofosbuvir + ledipasvir can be used with most ARV drugs. Because this therapy increases tenofovir levels when given as TDF, concomitant use requires considering renal function. The absolute tenofovir levels are highest, and may exceed exposure with established renal safety data. There is also insufficient data on safety for TDF co-administration with ritonavir- or cobicistat-containing regimens. If these drugs are being evaluated, consideration should therefore be given to changing the ARV drug regimen. If the combined use is unavoidable, renal monitoring is recommended during the treatment.

TAF may be an alternative to TDF during sofosbuvir + ledipasvir treatment for people receiving cobicistat or ritonavir as part of their ART. Ribavirin should not be used with zidovudine because the combination has been reported to increase the rates of anaemia. Before starting treatment, people should be evaluated for potential drug–drug interactions with selected antiviral medications by consulting the prescribing information and using other resources (such as <http://www.hep-druginteractions.org>).

Most of the recent or ongoing studies on HCV infection among children still follow a staggered approach. That approach delays the inclusion of younger children and therefore the approval for their weight or age band.

4.2 Proposed solutions

Include adolescents older than 12 years coinfecting with HIV and HCV in adult trials

Adolescents older than 12 years and weighing more than 35 kg can be usually treated with adult formulations. Adolescents should therefore be included in trials involving adults coinfecting with HIV and HCV to speed up the availability of HCV drugs in that age group.

A staggered approach is not needed in clinical trials involving children older than three years with HCV infection

A recent expert recommendation on how to speed up research on ARV drugs among children has envisioned the possibility of simultaneously enrolling different age cohorts by recommending that children other than infants (<2 years) should be recruited without a staggered approach if no specific concerns are present (35). This could also apply to HCV infection and HCV antiviral drugs.

Indication of new drugs for adolescents coinfecting with HIV and HCV

Indication of new drugs for adolescents coinfecting with HIV and HCV should be granted if the drug has been approved in HCV-monoinfected adolescents and there is enough evidence on safety in adults coinfecting with HIV and HCV.

4.3 Case study

Example of an adult trial that includes adolescents

There are some examples of randomized controlled trials that include adolescents older than 12 years at the same time as adults and with the same formulation. For example, an ongoing clinical trial of adults living with HIV also includes adolescents older than 12 years. The ADVANCE trial (ClinicalTrials.gov identifier: NCT03122262) intends to demonstrate that DTG + TAF + FTC is

equivalent to or better than DTG + TDF + FTC or EFV + TDF + FTC in first-line HIV treatment of adolescents 12 years or older.

4.4 Useful resources

- Guidelines for the screening, care and treatment of persons with hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016 (<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en>, accessed 22 May 2018)
- Chapter 5. Consolidated guidelines on the use of antiretroviral drugs for treating and prevention HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en>, accessed 22 May 2018).
- Recommendations for testing, managing, and treating hepatitis C. Arlington (VA): American Association for the Study of Liver Diseases and Infectious Diseases Society of America; 2017 (<http://www.hcvguidelines.org>, accessed 22 May 2018).



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5. SUMMARY

- Coinfections should be considered in developing ARV drugs and formulations for children, especially those that have a substantial epidemiological overlap with HIV, those that cause substantial morbidity and mortality among children living with HIV or those that are likely to have overlapping toxicity or clinically significant drug–drug interactions.
- Key coinfections to be considered in the process of developing ARV drugs and formulations for children include TB, HBV and HCV.
- Overarching major challenges introduced by coinfections include lack of appropriate formulations for children to treat coinfecting children, delays in initiating studies involving children and challenges with recruiting coinfecting children for these studies. This results in delayed or absent data with which to inform treatment.

6. KEY CONSIDERATIONS

- To ensure equitable and evidence-informed treatment of coinfecting children, the development of appropriate formulations and initiation of trials of ARV drugs among co-treated children must start much earlier than they do currently.
- Innovative strategies to retain coinfecting children in ARV drug studies should be incorporated into study designs.
- Other key solutions include facilitating more rapid recruitment for studies through specific resource investment in sites with a high burden of coinfecting children, pooling data from smaller studies when appropriate and using innovative analytical methods such as pharmacometrics.
- Close collaboration and improved coordination between disease areas are critical to addressing these challenges.

7. ACKNOWLEDGEMENTS

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