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ORIGINAL ARTICLE

Major revision version 12.0 of the European AIDS Clinical Society guidelines 2023

Juan Ambrosioni[1,2] | **Laura Levi**[3] | **Jasmini Alagaratnam**[4,5] | **Kathrin Van Bremen**[6] | **Andrea Mastrangelo**[7] | **Hylke Waalewijn**[8] | **Jean-Michel Molina**[3] | **Giovanni Guaraldi**[9] | **Alan Winston**[5] | **Christoph Boesecke**[6] | **Paola Cinque**[10] | **Alasdair Bamford**[11] | **Alexandra Calmy**[12] | **Catia Marzolini**[13,14,15] | **Esteban Martínez**[1,2] | **Cristiana Oprea**[16] | **Steven Welch**[17] | **Anna Koval**[18] | **Luis Mendao**[19] | **Jürgen K. Rockstroh**[6] | **The EACS Governing Board**

[1]HIV Unit, Infectious Diseases Service, Hospital Clinic-Fundació de recerca Clinic Barcelona – Institut de investigacions Biomediques August Pi i Sunyer, Barcelona, Spain

[2]CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain

[3]Department of Infectious Diseases, St-Louis and Lariboisière Hospitals, APHP, University of Paris Cité, Paris, France

[4]HIV Medicine & Sexual Health, Chelsea & Westminster Hospital NHS Foundation Trust, London, UK

[5]Section of Virology, Department of Infectious Disease, Imperial College London, London, UK

[6]Department of Medicine I, Bonn University Hospital, Bonn, Germany

[7]Allergology and Immunology Department, Centre Hopitalier Universitaire Vaudoise (CHUV), Lausanne, Switzerland

[8]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

[9]Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy

[10]Unit of Infectious Diseases, San Raffaele Scientific Institute, Milano, Italy

[11]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

[12]HIV/AIDS Unit, Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland

[13]Departments of Medicine and Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland

[14]Service of Clinical Pharmacology, University Hospital Lausanne and University of Lausanne, Lausanne, Switzerland

[15]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

[16]Infectious Diseases and HIV Department, Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

[17]Department of Paediatrics, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[18]University Medical Center Hamburg-Eppendorf, Germany

[19]European AIDS Treatment Group, Brussels, Belgium

Correspondence
Juan Ambrosioni, HIV Unit, Infectious Disease Service, Hospital Clinic-Fundació de recerca Clinic Barcelona – Institut de investigacions Biomediques August Pi i Sunyer, Villarroel 170, 08036, Barcelona, Spain.
Email: jambrosioni@intramed.net

Abstract

Background: The European AIDS Clinical Society (EACS) guidelines were revised in 2023 for the 19th time, and all aspects of HIV care were updated.

Key Points of the Guidelines Update: Version 12.0 of the guidelines recommend the same six first-line treatment options for antiretroviral treatment

(ART)-naïve adults as versions 11.0 and 11.1: tenofovir-based backbone plus an unboosted integrase inhibitor or doravirine; abacavir/lamivudine plus dolutegravir; or dual therapy with lamivudine or emtricitabine plus dolutegravir. The long-acting section has been expanded in the ART and drug–drug interaction (DDI) panels. Tables for preferred and alternative ART in children and adolescents have been updated, as has the section on prevention of vertical transmission, particularly with new guidance for breastfeeding. A new DDI table has been included for the ART and anti-infective drugs used for opportunistic infections, sexually transmitted infections, and other infectious conditions; lenacapavir has been included in all DDI tables. New sections on alcohol use and patient-reported outcome measures (PROMs) have been included in the comorbidity panel, in addition to updates on many relevant topics, such as new resource guidance for deprescribing in people with HIV. Other sections, including travel, cognitive impairment, cancer screening, sexual health, and diabetes have also been revised extensively. The algorithm for the management of acute hepatitis C virus infection has been removed, as current guidelines recommend immediate treatment of all people with recently acquired hepatitis C virus. Updates on vaccination for hepatitis B virus and recommendations for simplification to tenofovir-free two-drug regimens in people with isolated anti-hepatitis B core antibodies are provided. In the opportunistic infections and COVID-19 panel, guidance on the management of COVID-19 in people with HIV has been updated according to the most up-to-date evidence, and a new section on monkeypox has been added.

Conclusions: In 2023, the EACS guidelines were updated extensively and now include several new sections. The recommendations are available as a free app, in interactive web format, and as a pdf online.

KEYWORDS

antiretorviral therapy, ART, EACS, European AIDS Clinical, guidelines, HIV, major updates, Mpox, society, V12.0

INTRODUCTION

In 2023, the European AIDS Clinical Society (EACS) guidelines have been published for the 19th time. Version 12.0 comes at a time when the clinical management of people with HIV has substantially overcome the pressure imposed by the COVID-19 pandemic. Although COVID-19 continues to represent a significant challenge, the diagnosis, prevention, and management of COVID-19 in people with HIV vaccinated against SARS-CoV-2 is very similar to that in the general population, although people with HIV-induced severe immunosuppression remain at higher risk for poor clinical outcomes. However, this new version of EACS guidelines follows a new epidemic: monkeypox virus (MPXV). This infectious disease threat has once again disproportionally affected people with HIV or those most at risk of acquiring HIV. Indeed, MPXV can present as a very serious disease in people with HIV and severe immunosuppression, particularly those not on antiretroviral therapy (ART), and it has therefore been suggested that it should be considered an opportunistic infection in people with HIV. To respond to this new scenario, a new section has been included in the opportunistic infections panel, where the most relevant aspects of MPXV are discussed. The section on COVID-19 in people with HIV remains in the opportunistic infections panel, providing the most relevant specific information.

Since the last major guideline update in 2021, the HIV armamentarium has been enriched by new long-acting injectable drugs, including long-acting agents as an alternative for people with sensitive strains of HIV and a capsid inhibitor for treatment of multidrug-resistant HIV. Consequently, several sections have been expanded to provide updated information on the clinical use of cabotegravir

(CAB) and rilpivirine (RPV) and of lenacapavir (LEN); most changes are in the ART panel, but changes can also be seen in the drug–drug interaction (DDI) and other prescribing issues panel and other panels.

Since the 2021 revision, the EACS guidelines include recommendations on ART in children and adolescents, made in collaboration with Penta (formerly the Paediatric European Network for the Treatment of AIDS). Several major updates have been included in this section that are particularly related to the prevention of vertical transmission, to breastfeeding, and to the management of HIV infection in children and adolescents.

The aim of the EACS guidelines continues to be to provide easily accessible, systematic, and comprehensive recommendations across wide geographical settings. The development of version 12.0 has witnessed another major issue: the return of war in Europe. This sad scenario translates into several new challenges for people with HIV and healthcare providers: the availability of testing and care, provision of ART medication, displaced populations, and other threats. The EACS continues to aim to cover the needs of everyone with HIV infection in the different and heterogeneous, political, economic and healthcare conditions observed in different European regions and countries. Thus, some recommendations may offer broader choices than some national guidelines.

Lastly, EACS wants to promote the participation of community representatives and empower shared decision-making with healthcare professionals. Following the request of community representatives, and to emphasise person-centred language, all abbreviations to refer to people with HIV (notably 'PLWH' for people living with HIV) have been completely removed since version 11.1, launched in October 2022.

Version 12.0 consists of an overview table covering major aspects of HIV management and six main panels with more detailed recommendations on ART in adults and children, DDIs, drug dosage, prescribing in older individuals, diagnosis, monitoring and treatment of comorbidities, coinfections, COVID-19, and MPXV and other opportunistic infections. All sections have undergone major revisions.

The guidelines are available electronically in several different formats, including a free app for mobile devices, an interactive website, and a PDF online (www.eacsociety.org/guidelines/eacs-guidelines). Comments on the guidelines can be directed to guidelines@eacsociety.org.

METHODS

All recommendations in the EACS guidelines are continuously updated to ensure they cover the most relevant questions from everyday clinical practice.

The guidelines are developed based on evidence, and on expert opinion in any instances where evidence is not available [1]. The guidelines are reviewed by six panels of European HIV experts and governed by a leadership group consisting of a chair, a vice-chair, and a young scientist. Community representatives are included at all stages. Relevant new evidence is identified and selected by the panel members and discussed internally by each panel; cross-check meetings are later performed to ensure consistency of the content between panels and for approval of the whole content. The guidelines process is managed by the EACS guidelines chair and coordinator, working closely with the EACS secretariat and follows previous updates of the guidelines. Details have been previously published [1].

Formal revisions are made annually, with major revisions every other year and minor revisions in the years in between. The guidelines are published in the October and translated into several languages. Interim updates can be carried out in real time if new essential information is released in-between formal revisions. The main changes for version 12.0 in each section of the guidelines are summarized below. Access to the complete document is recommended for details [2].

ART panel

Version 12.0 has only two ART categories: recommended and alternative (see Table 1). EACS includes the same six recommended treatment options for first-line regimens for treatment-naïve adults as versions 11.0 and 11.1, which include triple-drug regimens consisting of tenofovir (either tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) with either 'lamivudine (3TC) or emtricitabine' (XTC) plus dolutegravir (DTG), bictegravir (BIC), raltegravir (RAL), or doravirine (DOR); abacavir (ABC)/3TC plus DTG; or dual therapy with XTC plus DTG. Doravirine remains among recommended regimens pending the results of head-to-head trials versus DTG. The alternative regimens, consisting of triple-drug tenofovir-based regimens with TAF or TDF + XTC in association with efavirenz (EFV), RPV or boosted darunavir (DRV/b), are to be used when none of the recommended regimens are feasible [1].

For virologically suppressed people, bi-monthly injections with long-acting CAB (CAB-LA) plus RPV-LA have been confirmed as a switch option non-inferior to monthly injections (which are not available in Europe) up to 152 weeks, although there were numerically more cases with detectable viral load in the bi-monthly injection arm (2.7% vs. 1%; difference of 1.7%; 95% confidence interval [CI] 0.1%–3.3%) [3]. The use of an oral lead-in to evaluate safety and tolerability remains optional. Baseline factors that could be associated with virological failure when

TABLE 1 Preferred and alternative antiretroviral regimens for treatment-naïve adults with HIV.

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
Two NRTIs + INSTI		
ABC/3TC + DTG or ABC/3TC/DTG	HLA-B*57:01 negative, HBsAg negative	(I) ABC: HLA-B*57:01, cardiovascular risk, (II) Weight increase (DTG)
TAF/FTC/BIC		(II) Weight increase (BIC, TAF)
TAF/FTC or TDF/XTC + DTG		(II) Weight increase (DTG, TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing
TAF/FTC or TDF/XTC + RAL qd or bid		(II) Weight increase (RAL, TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing, (IV) RAL: dosing
One NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative, HIV VL <500 000 copies/mL	(II) Weight increase (DTG), (V) Not recommended after PrEP failure
Two NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		(II) Weight increase (TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing, (VI) DOR: HIV-2
Alternative regimens		
Two NRTIs + NNRTI		
TAF/FTC or TDF/XTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	(II) Weight increase (TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing, (VII) EFV: neuropsychiatric adverse events. HIV-2 or HIV-1 group 0, dosing
TAF/FTC or TDF/XTC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count >200 cells/μL, HIV VL <100 000 copies/mL, not on gastric pH increasing agents, with food	(II) Weight increase (TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing, (VIII) RPV: HIV-2
Two NRTIs + PI/r or PI/c		
TAF/FTC or TDF/XTC + DRV/c or DRV/r or TAF/FTC/DRV/c	With food	(II) Weight increase (TAF), (III) TDF: prodrug types. Renal and bone toxicity. TAF dosing, (IX) DRV/r: cardiovascular risk, (X) Boosted regimens and drug–drug interactions

Note: Additional guidance: (I) ABC contraindicated if HLA-B*57:01 positive, not to be used for same-day start. Even if HLA-B*57:01 is negative, counselling on the risk of a hypersensitivity reaction is mandatory. ABC should be used with caution in people with a high CVD risk (>10%). (II) Treatment with INSTIs or TAF may be associated with weight increase. (III) In certain countries, TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate). Generic forms of TDF are available, which use phosphate, maleate, and succinate salts instead of fumarate. They can be used interchangeably. When available, combinations containing TDF can be replaced with the same combinations containing TAF. TAF is used at 10 mg when coadministered with drugs that inhibit P-glycoprotein and at 25 mg when coadministered with drugs that do not inhibit P-glycoprotein. The decision whether to use TDF or TAF depends on individual characteristics and availability. If the ART regimen does not include a booster, TAF and TDF have a similar short-term risk of renal adverse events leading to discontinuation and bone fractures. TAF should be considered as a first choice (expert opinion, pending clinical trial) over TDF in individuals with: (1) established or high risk of chronic kidney disease; (2) coadministration of medicines with nephrotoxic drugs or prior TDF toxicity; (3) osteoporosis/progressive osteopenia, high FRAX score or risk factors; or (4) history of fragility fracture. (IV) RAL can be given as RAL 400 mg bid or RAL 1200 mg (two × 600 mg tablets) qd. Note: RAL qd should not be given in the presence of an inducer (i.e. tuberculosis drugs, antiepileptics) or divalent cations (i.e. calcium, magnesium, iron), in which case RAL should be used bid. (V) HIV infections occurring in the context of PrEP failure may be associated with resistance-associated mutations. (VI) DOR is not active against HIV-2. DOR has not been compared with an INSTI and was shown to be non-inferior to EFV and DRV. There is a risk of resistance-associated mutations in case of virological failure. Results of genotypic resistance testing are necessary before starting DOR. (VII) EFV is not to be given in a history of suicide attempts or mental illness; 400 or 600 mg daily should be used; if a rifampicin-based regimen for tuberculosis is used, dosing must be 600 mg; EFV is not active against HIV-2 and HIV-1 group O strains. (VIII) RPV is not active against HIV-2. (IX) A single large study has shown an increased CVD risk with cumulative use of DRV/r; this has not been confirmed in other studies. DRV/r should be used with caution in people with a high CVD risk. (X) Boosted regimens with RTV or COBI are at higher risk of drug–drug interactions. Adapted from EACS guidelines v.12.0.

Abbreviations: /c, boosted by cobicistat; /r, boosted by ritonavir; 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BIC, bictegravir; bid, twice daily; COBI, cobicistat; CVD, cardiovascular disease; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; FRAX, Fracture Risk Assessment Tool; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HLA human leukocyte antigen; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; PrEP, pre-exposure prophylaxis; qd, four times daily; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; XTC, lamivudine or emtricitabine.

combined should be identified before starting CAB-LA + RPV-LA and include archived RPV-associated mutations, HIV-1 subtype A6/A1, and a body mass index >30 kg/m^2 [4]. In the clinical trials evaluating CAB-LA + RPV-LA, viral load monitoring was performed every 2 months, with each injection. Although no intensified viral load monitoring has been specifically recommended in this setting, panel members recommend it should be done at least every 3–6 months, and close attention must be paid to optimal administration and timeframe. It is also critical to ensure patients have protective anti-hepatitis B surface (HBs) antibodies and no HBs antigen before switching to CAB-LA + RPV-LA.

The section on virological failure has been updated and includes subcutaneous LEN, with oral lead-in, as a new treatment option in combination with optimised background regimen in people with multidrug-resistant HIV-1 infection.

For treatment of women with HIV who are pregnant or considering pregnancy, the updated guidelines now recommend that the ART regimen should be individualised, taking into account women's preferences, tolerability, the potential risk from ART exposure, and suboptimal pharmacokinetics in pregnancy. The combination of ABC and 3TC has been now downgraded from a recommended to an alternative regimen in treatment-naïve pregnant women because of an unfavourable risk/benefit ratio. Only three treatment options are recommended as first-line regimens for ART-naïve pregnant women, including triple-drug regimens consisting of tenofovir (either TDF or TAF) with either XTC plus DTG 50 mg daily, RAL 400 mg twice daily (bid), or boosted darunavir/ritonavir (DRV/r) 600/100 mg bid. All restrictions to the use of TAF or DTG in pregnant women have been now removed because of a favourable risk/benefit ratio in recent studies [5].

For people with HIV and tuberculosis coinfection, the guidelines are aligned with the updated guidelines of the World Health Organization (WHO) and therefore recommend that ART should be started as soon as possible (within 2 weeks of initiating tuberculosis treatment) regardless of CD4 count, with the exception of tuberculosis meningitis.

The section on pre-exposure prophylaxis (PrEP) has been extensively revised. CAB-LA is included for the first time on application to compassionate use for individuals for whom TDF/FTC or TAF/FTC are contraindicated (such as people with advanced renal failure), pending approval from the European Medicines Agency [6]. Low adherence to PrEP, which should trigger post-exposure prophylaxis, has been explicitly defined.

Vaccination against hepatitis A and B, human papillomavirus, and MPXV should be offered to all PrEP users, and the current evidence also supports doxycycline prophylaxis (200 mg within 24–72 h post condomless sex) on a case-by-case basis in those with repeated sexually transmitted infections (STIs) with the caveat that the long-term effects on microbiota and STI resistance are unknown.

DDI and other prescribing issues panel

The DDI tables, which provide an overview of the interaction potential between individual antiretroviral drugs and the most commonly used comedications within a therapeutic area, have been expanded to include DDIs with the anti-infective drugs to treat STIs and opportunistic infections, including, among others, MPXV. The COVID-19 DDI table has been updated to remove most monoclonal antibodies as they do not retain antiviral efficacy against the current SARS-CoV-2 subvariants and are no longer recommended by international COVID-19 treatment guidelines.

The long-acting injectable antiretroviral drug LEN has been added to all DDI tables. LEN is not impacted to a clinically significant extent by strong cytochrome P450 (CYP)-3A4 inhibitors (except dual CYP3A4 and UGT1A1 inhibitors, e.g., atazanavir); however, strong or moderate inducers (e.g., rifampicin) can substantially reduce LEN exposure and so are not recommended. On the other hand, LEN is a moderate inhibitor of CYP3A4, so caution is required with sensitive CYP3A4 substrates (e.g., ergot derivatives) during coadministration and during the initial weeks after LEN discontinuation as it remains in the circulation for a prolonged period.

The section on CAB-LA and RPV-LA has been expanded to include factors that can potentially impact the drug release from the depot (i.e., site of injection, exercise) as well as factors that can increase the risk of virological failure, as mentioned in ART panel updates [4]. This section also includes dosing recommendations in case of missed injections.

The prescribing resources for the management of older people with HIV have been further developed to include non-HIV drugs to deprescribe in the presence of certain conditions. Deprescribing aims to reduce pill burden, drug toxicities, falls, hospital admission, and mortality and to improve health-related quality of life [7].

Detailed information on DDIs can be found in the University of Liverpool website (www.hiv-druginteractions.org), and real-life experiences on the clinical management of DDIs can be obtained from https://clinicalcasesddis.com.

Comorbidity panel

Preventing and managing non-infectious comorbidities in people with HIV continues to be a major focus of the

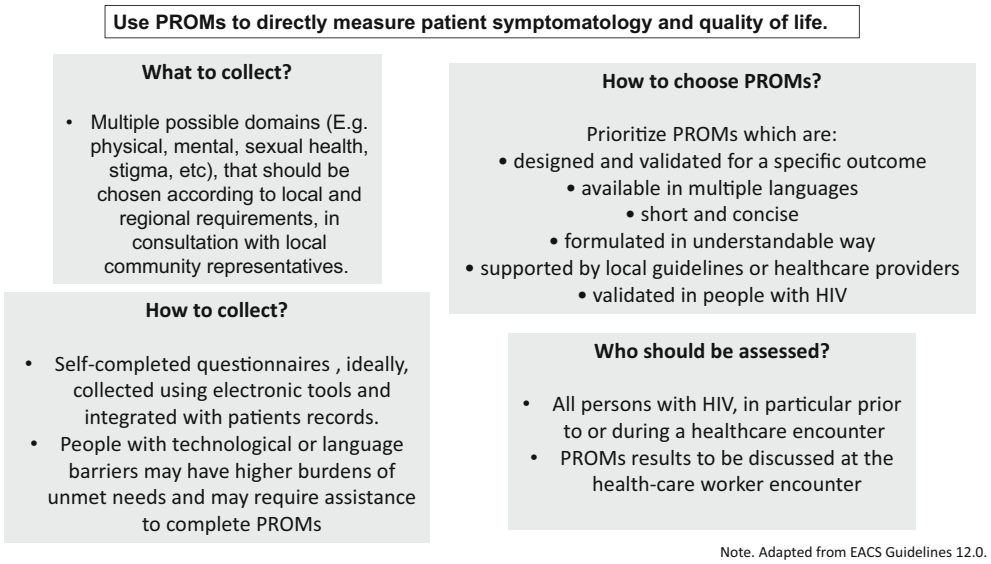

FIGURE 1 The use of patient-reported outcomes measures (PROMs) in clinical practice in the setting of HIV consultation.

guidelines. For many years, this section has been the largest section, and this update includes new sections and substantial revisions to existing sections.

A new section on patient-reported outcome measures (PROMs) has been added (Figure 1). This section acknowledges that PROMs have been used in HIV clinical care for many years and recommends that PROMs on quality of life be considered in clinical practice. Existing PROMs included in the guidelines are highlighted, for instance, depression questionnaires, anxiety screening questionnaires, and cognitive health screening questionnaires (validated questionnaires can be found on the PROMIS website: www.healthmeasures.net/explore-measurement-systems/promis). The utility of including a quality-of-life questionnaire is recommended to ensure the fourth 90 in the HIV cascade of care – that is, the need to focus on optimising quality of life in people living with HIV – is addressed [8]. A fundamental aspect of all PROMs is ensuring that completed questionnaires are addressed and reviewed during clinical encounters.

A section on alcohol use and management has been added to the guidelines. Evidence suggests that identification of at-risk drinking and alcohol use disorders and advice on alcohol consumption among at-risk drinkers and those with alcohol-related problems are effective in reducing consumption. Given that alcohol-related disorders are the most frequently observed substance use disorders, this is a welcome addition to the guidelines. Both brief interventions aiming to reduce a person's alcohol consumption and motivational interviewing techniques are outlined.

In addition to these new sections, all existing sections have been revised, with substantial revisions to several current sections. The section on cognitive health has been renamed 'The Algorithm for Diagnosis and Management of Cognitive and Central Nervous System Neurological Symptoms' to widen the breadth of symptomatology this section covers. The rationale here is that this more holistic approach covers other symptomatology that may present in individuals with cerebrospinal fluid HIV RNA escape. The new HIV-associated brain injury criteria are also introduced [9].

Several changes to the sexual and reproductive health section have been incorporated: the U=U (undetectable = untransmittable) wording has been modified; the mention that prophylaxis for bacterial STIs may be considered has been included; MPXV information and diagnosis has been referenced to the opportunistic infections section. Substantial modifications were made to the syphilis treatment section so it is in keeping with other European guidelines.

Other modifications include the following:

- lifestyle interventions sections: substantially shortened to ensure the guidelines are as succinct as possible
- diabetes section: highlighting that metformin is no longer considered a first-line therapy for type 2 diabetes mellitus
- hypertension section: outlining that hypertension detected in clinic should be confirmed with home blood pressure monitoring
- chronic lung disease section: updates on the treatment for chronic obstructive pulmonary disease to be consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 recommendations (www.goldcopd.org)
- cancer-screening section: recommendations to include high-resolution anoscopy in addition to anal cytology for anal cancer screening.

Viral hepatitis coinfection panel

The recommendations for people with HIV and hepatitis B virus (HBV) coinfection have been updated regarding HBV relapse/viral breakthroughs as there is an increased use of ART regimens, including drugs with a lower genetic barrier (without TDF/TAF) or even without activity against HBV (without TDF/TAF and without 3TC/FTC). Caution must be taken when switching from a TDF/TAF-based regimen to drugs with a lower genetic barrier for HBV, for example, FTC or 3TC. This must also be considered individually in people with isolated anti-hepatitis B core antibodies as there may be a risk of viral breakthrough or relapse of HBV in some circumstances. Some people with HIV have known impaired immune responses to current HBV vaccines. A recently approved vaccine (containing virus surface antigen together with an adjuvant consisting of a toll-like 9 receptor agonist, CpG-ODN) should be considered to obtain better responses in people with HIV with no responses to previous vaccinations.

The recommendations for hepatocellular carcinoma (HCC) screening in people with HIV and viral hepatitis coinfection have also been updated. The PAGE-B score has been validated for Caucasian people with HIV and should be used for HCC screening in people with HIV and HBV coinfection [10].

Since the publication of the last version of these guidelines, there has been no licensing of new direct-acting antivirals for the treatment of hepatitis C virus (HCV). In the recommendations for recently acquired HCV infection, the figure about the algorithm for recently acquired HCV infection has been deleted because version 12.0 recommends immediate treatment of all people with HIV with recently acquired HCV [11]. Thus, everyone with detectable RNA for HCV should be considered for therapy with the currently recommended regimens (Table 2).

After the licensing of bulevirtide and the first data in people with HIV/HBV/hepatitis D virus (HDV) coinfection, which have shown reduced HDV RNA and normalisation of liver transaminases, subcutaneous bulevirtide 2 mg/day in combination with TDF/TAF should be used in people with HDV RNA with HIV with compensated liver disease. The optimal duration of treatment remains unclear, and further data are awaited. Meanwhile, such people should be treated in large centres by physicians experienced with this treatment and access to studies in this area.

Opportunistic infections and COVID-19 panel

The evolving landscape of classic and new opportunistic diseases demanded several modifications to the opportunistic infections and COVID-19 section.

The most evident change was the addition of a new section covering the epidemiology, clinical manifestations, and management of MPXV. Although people with good immunological status and without HIV can present with MPXV, the decision to include this (mostly) sexually transmitted disease into the opportunistic infections panel was made following recent evidence suggesting a more severe and life-threatening course of MPXV in people with undiagnosed, untreated, or advanced HIV infection. Complications observed in these people include a more aggressive clinical course of MPXV and more frequent secondary complications, such as severe lesion superinfection and sepsis [12]. MPXV is also discussed in the STIs section of the comorbidity panel and in the vaccination section for people with HIV and receiving PrEP.

Two major modifications to the treatment strategies for classic opportunistic infections were implemented in this version of the guidelines:

1. Trimethoprim-sulfamethoxazole has been added as an additional 'preferred' regimen for the treatment of toxoplasma encephalitis. This recommendation stems from the accumulating evidence suggesting that trimethoprim-sulfamethoxazole is most likely equally effective, more available, and possibly safer than other therapeutic options [13].
2. The current WHO recommendation for a single-dose liposomal amphotericin B + flucytosine + fluconazole regimen has been included as an additional 'preferred' therapeutic option in cryptococcal meningitis (CM) [14]. This modification was motivated by the fact that access to liposomal amphotericin B is not uniform across European countries and that the application of the current standard-of-care regimen in high-income countries (i.e., 14 days of liposomal amphotericin B + flucytosine) may not be feasible in many contexts. Therefore, even though the effectiveness of the single-dose liposomal amphotericin B + flucytosine + fluconazole regimen has not been formally compared to the standard of care in high-income countries, the panel deemed it important to include this therapeutic option.

Similarly, a new alternative regimen of liposomal amphotericin B + miltefosine has been added as a therapeutic option in visceral leishmaniasis following results from a recent trial [15] and updates from WHO guidelines [16].

Additional modifications were also applied to the recommendations on ART initiation in the context of specific opportunistic infections. For most opportunistic infections, ART initiation remains recommended early (within 2 weeks of diagnosis of the opportunistic infections). For tuberculous meningitis (TM) and CM, the

TABLE 2 Preferred direct-acting antiviral hepatitis C virus (HCV) treatment options for people with HIV/HCV coinfection (except for people pre-treated with protease or NS5A inhibitors).

		Treatment duration and RBV usage		
HCV GT	**Treatment regimen**	**Non-cirrhotic**	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 and 4	EBR/GZR	12 weeks[a]	12 weeks[a]	Not recommended
	GLE/PIB	8 weeks	8–12 weeks[b]	Not recommended
	SOF/VEL	12 weeks	12 weeks	12 weeks with RBV[i]
	SOF/LDV ± RBV	8–12 weeks without RBV[c]	12 weeks with RBV[d]	12 weeks with RBV[i]
2	GLE/PIB	8 weeks	8–12 weeks[b]	Not recommended
	SOF/VEL	12 weeks	12 weeks	12 weeks with RBV[i]
3	GLE/PIB	8 weeks[e]	8–12 weeks[b,e]	Not recommended
	SOF/VEL ± RBV	12 weeks[f]	12 weeks with RBV[g]	12 weeks with RBV[i]
	SOF/VEL/VOX	-	12 weeks	Not recommended
5 and 6	GLE/PIB	8 weeks	8–12 weeks[b]	Not recommended
	SOF/LDV ± RBV	12 weeks ± RBV[h]	12 weeks with RBV[d]	12 weeks with RBV[i]
	SOF/VEL	12 weeks	12 weeks	12 weeks with RBV[i]

Note: Adapted from EACS guidelines v.12.0.

Abbreviations: EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; PIB, pibrentasvir; RAS, resistance-associated substitutions; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

[a]In people with HIV with GT1a with baseline HCV RNA <800 000 IU/mL and/or absence of NS5A RASs, as well as in treatment-naïve people with HIV with GT4 with HCV RNA <800 000 IU/mL. In GT1b treatment-naïve people with HIV with F0–F2 fibrosis, 8 weeks can be considered.

[b]8 weeks of treatment can be considered in treatment-naïve people with HIV.

[c]8 weeks of treatment without RBV only in treatment-naïve people with HIV with F <3 and baseline HCV RNA <6 million IU/mL.

[d]RBV can be omitted in treatment-naïve or treatment-experienced people with HIV with compensated cirrhosis without baseline NS5A RAS. In those intolerant to RBV, treatment may be prolonged to 24 weeks.

[e]Treatment duration in HCV GT3 for whom previous treatment with interferon and RBV ± SOF or SOF and RBV failed should be 16 weeks.

[f]In treatment-experienced people with HIV, RBV should be added unless NS5A RASs are excluded; if these people are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV.

[g]If RAS testing is available and demonstrates absence of NS5A RAS Y93H, RBV can be omitted in treatment-naïve people with HIV with compensated cirrhosis.

[h]In treatment-experienced people (exposure to interferon/RBV/SOF) with HIV, add RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV.

[i]In people intolerant to RBV, treatment may be prolonged to 24 weeks.

benefit of early ART initiation needs to be weighed against the possible adverse effects of immune reconstitution, accumulating pharmacological toxicities, and DDIs. Several trials in resource-limited settings have shown that early initiation of ART in CM [17] and TM [18] may be detrimental. However, as also suggested by recent observational evidence [19], these results may not be generalized to high-resource settings, in which disease may be less severe at presentation and optimal antimicrobial treatment, early recognition of clinical deterioration, and prompt corrective measures can be ensured. In the absence of data from randomized clinical trials in high-income settings, the indication for an early ART start in CM and TM cannot be generalized. However, building on the above-mentioned considerations, recommendations for ART initiation in TM were reformulated to underscore that the timing of ART introduction should take into account the context of care and that ART could be started earlier in specific circumstances. For CM, while leaving unchanged the recommended timing for ART start, the panel agreed to add a comment to support considering earlier initiation of ART on an individual basis in high-income settings.

Finally, the COVID-19 section has been reduced and updated following the recent developments of the pandemic, and cross-references to a newly created ART/anti-infectives interaction table have been added throughout the text.

Paediatric HIV treatment and prevention of vertical HIV transmission panel

This collaborative section between Penta and EACS continues to evolve and aims to harmonise paediatric and adult ART guidance. The paediatric section provides

TABLE 3 Preferred and alternative first-line antiretroviral options in children and adolescents.

	Backbone		Anchor drug (in alphabetical order)	
Age	**Preferred**	**Alternative**	**Preferred**	**Alternative**
0–4 weeks	ZDV[a] + 3TC	-	LPV/r[c,d]	RAL[d]
	ABC + 3TC		NVP[d]	
4 weeks–3 years	ABC[b] + 3TC[e]	ZDV + 3TC[h]	BIC[j]	LPV/r
	TAF[f] + XTC[g]	TDF[i] + 3TC	DTG[k]	NVP
				RAL
3–6 years	ABC[b] + 3TC[e]	TDF[i] + XTC	BIC[j]	DRV/r
	TAF[f] + XTC[g]	ZDV + XTC	DTG[k]	EFV
				LPV/r
				NVP
				RAL
6–12 years	ABC[b] + 3TC[e]	TDF[i] + XTC	BIC[j]	DRV/r
	TAF[f] + XTC[g]		DTG[k]	EFV
				ELV/c
				RAL
>12 years	ABC[b] + 3TC[e]	TDF[i] + XTC	BIC[j]	DRV/b[l]
	TAF[f] + XTC[g]		DTG[k]	EFV[l]
				RAL[l]
				RPV[l]

Note: Adapted from EACS guidelines v.12.0. Considerations specific to paediatric ART are described in the footnotes below.

Abbreviations: /c, boosted by cobicistat; /r, boosted by ritonavir; 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BIC, bictegravir; DHHS, Department of Health and Human Services; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; EVG, elvitegravir; FDC, fixed-dose combinations; FTC, emtricitabine; HLA, human leukocyte antigen; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; WHO, World Health Organization; XTC, lamivudine or emtricitabine; ZDV, zidovudine.

[a]In view of potential long-term toxicity, any child on ZDV should be switched to ABC or TAF (preferred) or TDF (alternative) once an increase in age and/or weight makes licensed formulations available.

[b]ABC should NOT be prescribed to HLA-B*57:01-positive individuals (where screening is available). ABC is not licensed under 3 months of age, but dosing data for younger children are available from the WHO and DHHS.

[c]LPV/r should not be routinely administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days, although it may be considered if there is a risk of transmitted NVP resistance and appropriate INSTI formulations are unavailable. In these circumstances the neonate should be monitored closely for LPV/r-related toxicity (cardiac, metabolic, endocrine).

[d]If starting a non-DTG anchor drug in the neonatal period, it is acceptable to continue this option. However, when over 4 weeks and 3 kg, a switch to a second-generation INSTI (DTG or BIC) is recommended if and when an appropriate licensed formulation is available. If initially commenced on RAL and appropriate DTG or BIC formulations are not predicted to be available in a suitable timeframe, then an interim switch to LPV/r could be considered to remove the risk of developing INSTI resistance while awaiting the availability of DTG (or BIC).

[e]At HIV VL >100 000 copies/mL, ABC + 3TC should not be combined with EFV as anchor drug.

[f]TAF is currently licensed in Europe for children and adolescents in the following FDCs: TAF/FTC (10/200 mg or 25/200 mg) from 12 years and 35 kg; TAF/FTC/EVG/c (10/200/150/150 mg) from 2 years and 14 kg; TAF/FTC/BIC (25/200/50 mg) from 25 kg; TAF/FTC/BIC (15/120/30 mg) from 2 years and between 14 and 25 kg. When TAF becomes licensed in younger ages and weights, it should be included as a preferred option. TAF has been associated with excessive weight gain in adults, especially in combination with DTG. This has not yet been demonstrated in paediatric and adolescent observational studies or trials; however, its possibility should be considered when TAF is used. Families and young people should be counselled regarding this, and weight should be monitored. DTG remains the preferred anchor drug due to superior efficacy.

[g]XTC indicates circumstances when FTC or 3TC may be used interchangeably.

[h]If using NVP as an anchor drug in children aged 2 weeks to 3 years, consider using three NRTI backbones (ABC + ZDV + 3TC) until VL consistently <50 copies/mL.

[i]TDF is only licensed from 2 years of age. In view of concerns about a potential impact on bone development and renal toxicity, TAF is recommended over TDF at all ages in settings where this is licensed and available.

[j]BIC is currently licensed in Europe for children and adolescents in the following FDCs: TAF/FTC/BIC (25/200/50 mg) from 25 kg; TAF/FTC/BIC (15/120/30 mg) from 2 years and between 14 and 25 kg. When BIC becomes licensed in younger ages and weights, it can be included as a preferred option.

[k]DTG is licensed from 4 weeks and 3 kg. When DTG becomes licensed at younger ages and weights, it can be included as a preferred option. Dispersible ABC/3TC/DTG tablets have been recently licensed for children between 14 and 25 kg in Europe. Specific caution should be taken when prescribing dispersible DTG as it is not bioequivalent to film-coated tablets. DTG has been associated with excessive weight gain in adults, especially in combination with TAF. This has not yet been demonstrated in paediatric and adolescent observational studies or trials; however, its possibility should be considered when DTG is used. Families and young people should be counselled regarding this, and weight should be monitored.

[l]Due to predicted poor adherence in adolescence, if the preferred anchor drugs (BIC or DTG) are not available/appropriate, then – of the possible alternative third-line agents – DRV/b is favoured due to a higher barrier to resistance than in EFV, RAL, or RPV.

updated guidance on preferred and alternative first-line combinations for children, taking into account new data and the availability of formulations for use in Europe (Table 3). Guidance on the consideration of PrEP and LA agents in adolescents has been included. Guidance on the use of dual therapy has been modified, and treatment options in the context of HIV and tuberculosis coinfection have been updated.

The most significant addition is a new section on postnatal prophylaxis and infant feeding. While acknowledging that practice currently varies across Europe, general principles have been provided on transmission risk stratification, choice and duration of infant postnatal prophylaxis, decision-making around infant feeding and supported breastfeeding, and infant HIV testing and monitoring. If specific criteria are met, including optimal maternal ART adherence, suppressed viral load, and availability of regular multi-disciplinary team support and frequent viral load monitoring, then the option of supported breastfeeding should be provided. In some countries, infant PrEP is offered for the duration of supported breastfeeding; in others, only the usual post-birth regimen is recommended. During supported breastfeeding, multi-disciplinary team support should be easily accessed throughout and especially during times of complications such as detectable maternal viral load, mastitis, or other intercurrent illness of the mother or the infant.

As in the previous version, a link to refer cases to the Penta virtual clinic is provided [20]. This virtual multidisciplinary team welcomes referrals relating to HIV treatment in children and adolescents as well as antenatal and postnatal management in relation to the prevention of vertical HIV transmission.

Perspectives

The field of HIV continues to evolve in Europe and worldwide. Adults diagnosed early with HIV infection and starting early ART have a life expectancy near that of the general population [21], and HIV transmissions are declining in some European settings. Thus, the population of people with HIV in Europe will increase the median age. New challenges will emerge in the management of comorbidities and new needs will become evident; solutions to those problems will evolve in parallel, as convenient ART administration routes for everybody and optimal therapy for comorbid conditions and coinfections. Moreover, following the major impact of the COVID-19 and MPXV outbreaks, future outbreaks and pandemics may place significant strain on HIV prevention and management. This natural evolution will also require a continuous process of updating the recommendations provided by these guidelines for professionals managing HIV infection and related conditions, in a practical and simple way.

CONCLUSIONS

The EACS guidelines underwent major revisions of all sections in 2023 and were expanded with recommendations on MPXV and the use of PROMs in clinical practice. The guidelines are available as a free app, interactive web version, and online pdf.

AUTHOR CONTRIBUTIONS

Juan Ambrosioni, Laura Levi, Catia Marzolini, Jasmini Alagaratnam, Kathrin Van Bremen, Andrea Mastrangelo, Hylke Waalewijn, and Jürgen K. Rockstroh prepared the first draft of the manuscript. All authors have seen, corrected, and approved the final version.

CONFLICT OF INTEREST STATEMENT

Declarations of interest of all panel members are available upon request. Please contact info@eacsociety.org. Juan Ambrosioni has received personal fees from and participated in advisory boards for ViiV, Gilead, Janssen, and MSD; has received funding for research from ViiV, Gilead, and MSD; and has been a member of data safety monitoring boards for HIPRA and Grifols, all outside the current work. Jasmini Alagaratnam has received financial support to attend scientific conferences from MSD and Gilead. Kathrin Van Bremen has received honoraria or consultation fees from Gilead, ViiV, and MSD. Jean-Michel Molina has received grants from Gilead and MSD for ANRS projects paid to the institution and advisory board fees from MSD and ViiV. Giovanni Guaraldi has received research grants and personal fees for consulting or speaking at educational events from Gilead, MSD, Janssen, and ViiV. Alan Winston has received grants from ViiV, Gilead, and MSD; has received honoraria from ViiV, Gilead, Janssen, and MSD; and has participated in speakers' bureaux for ViiV, Gilead, Janssen, and MSD. Christoph Boesecke has received honoraria for lectures and/or consultancies from AbbVie, Gilead, Janssen, MSD, and ViiV and funding from Dt. Leberstiftung, DZIF, Hector Stiftung, and NEAT ID. Paola Cinque has received grants from Gilead and consultation fees from Pfizer, Cellevolve, Shire, Excision, and Exevir. Alasdair Bamford has received personal fees for consulting from Gilead. Alexandra Calmy has received educational grants from MSD and Gilead paid to the institution. Catia Marzolini has received speaker honoraria from ViiV, Gilead, MSD, and Pfizer. Esteban Martínez has received grants from ViiV and consultation fees from ViiV, Gilead, MSD,

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ORCID

Juan Ambrosioni https://orcid.org/0000-0001-9931-6686
Jasmini Alagaratnam https://orcid.org/0000-0003-2256-423X
Hylke Waalewijn https://orcid.org/0000-0002-5135-8729
Giovanni Guaraldi https://orcid.org/0000-0002-5724-3914
Alan Winston https://orcid.org/0000-0002-5847-8416
Paola Cinque https://orcid.org/0000-0003-2448-5957
Alasdair Bamford https://orcid.org/0000-0003-4764-229X
Cristiana Oprea https://orcid.org/0000-0001-9581-2527

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