Dual Antiretroviral Regimens for HIV—Here to Stay

Catherine Creticos M.D. [1,2]

[1] Metro Infectious Disease Consultants, Chicago, IL, USA
[2] Howard Brown Health, Chicago, IL, USA
* Corresponding author: creticos@uic.edu

Submitted: 31 May 2022, accepted: 20 June 2022, published: 30 September 2022

Abstract: It has been twenty-five years since antiretroviral therapy (ART) for human immunodeficiency virus (HIV) became available. Treatment has evolved substantially over these decades to become highly effective and produce substantial improvements in morbidity and mortality for people with HIV. The standard of care has been three-drug regimens (3DRs) which include three drugs active against HIV, occasionally with a fourth drug added as a booster agent. Efforts to provide potentially safer or more convenient treatment regimens for people with HIV have served as the impetus to relook at two drug regimens (2DRs). Several studies have led to the establishment of 2DRs as real options for many patients. This review summarizes clinical data for the established 2DRs and explores some of the remaining questions and concerns about these regimens.

Keywords: Human Immunodeficiency Virus (HIV); antiretroviral therapy (ART); two-drug regimen

How to cite: Creticos, C. Dual Antiretroviral Regimens for HIV—Here to Stay. *Priv. Pract. Infect. Dis.*, 2022, 2(3): 9; doi:10.55636/ppid2030009.

1. Introduction

The treatment of Human Immunodeficiency Virus has undergone many changes since the introduction of the first FDA-approved drug, zidovudine, in 1987 [1], which was initially used in high doses as monotherapy. As additional drugs were introduced, the combination of two nucleoside reverse transcriptase inhibitors (NRTIs) showed greater viral suppression than monotherapy but only slowed disease progression for a short time and at the expense of greater toxicities [2]. New combinations became possible with the advent of the first FDA-approved protease inhibitor (PI) in December 1995, and the approval of drugs in the non-nucleoside reverse transcriptase inhibitor class. Soon thereafter,

the combination of two NRTIs with a drug from one of these new classes brought a paradigm shift to treatment because adequate and sustained virologic suppression could be achieved, with subsequent immune reconstitution and survival benefits [1,2]. However, these initial highly active regimens were plagued by the complexity of the regimens and high levels of drug toxicity, leading to regimen failures and the development of antiretroviral resistance. Despite the initial lack of long-term success of two-drug NRTI combination therapy, the search for a dual-drug regimen that has sustained efficacy and low toxicity has continued. Dual-drug regimens are attractive because exposing patients to fewer drugs may reduce drug toxicities overall, including those not yet evident that may arise after a longer duration of exposure; reduce drug–drug interactions, especially important for people with HIV with comorbidities; and possibly reduce costs.

2. Methods

A search of PubMed was conducted for publications of review articles, clinical trials, and observational studies including the following terms and abbreviations: HIV, Dual drug therapy, Two drug regimen, Simplification, Antiretroviral therapy, Switch study, Treatment experience, Naïve to therapy, and Test-to-Treat. The following guidelines were also consulted: DHHS, Department of Health and Human Services, Washington DC, USA; EACS, European Aids Clinical Society, Brussels, Belgium; GeSIDA, Grupo De Estudio De Sida, Madrid, Spain. This literature search started in March 2022 and ended May 2022 and included scientific data published between January 1996 and May 2022.

2.1. Efficacy

The efficacy of a regimen remains one of the primary goals of ART. For a 2DR to be considered as an alternative to a 3DR, similar efficacy is necessary. Several clinical trials have been designed with efficacy and non-inferiority of a 2DR vs. a 3DR as a primary endpoint. Table 1 summarizes the trials that are discussed in this article.

Table 1: 2 Drug Regimen vs 3 Drug Regimen Comparator Trials

Clinical Trial	2DR Arm	Comparator	Subject Population	Sample Size	Follow-Up	Virologic Response in 2 Arm vs. Comparator
GARDEL	LPV/r+3TC	LPV/r+2NRTIs	Naïve to ART	214 vs. 202	48 weeks	88.3% vs. 83.7%
ATLAS-M	ATV/r+3TC	ATV/r+2NRTIs	Suppressed	133 vs. 133	48 weeks	80.5% vs.79.7%
DUALIS	DTG+bDRV	DRV-based 3DR	Suppressed	131 vs. 132	48 weeks	86.3% vs.87.9%
SWORD 1 & 2	DTG+RPV	3DR	Suppressed	516 vs. 512	48 weeks	95.0% vs. 95.0%
GEMINI 1 & 2	DTG+3TC	DTG+FTC/TDF	Naïve to ART	719 vs. 722	48 weeks	91.0% vs. 93.0%
TANGO	DTG+3TC	TAF-based 3DR	Suppressed	369 vs. 372	48 weeks	93.2% vs. 93.0%
SALSA	DTG+3TC	3DR or 4DR	Suppressed	246 vs. 247	48 weeks	94.0% vs. 93.0%
FLAIR & ATLAS	CAB+RPV	DTG/3TC/ABC or 2NRTS+3rd drug	Pretreated, Suppressed	591 vs. 591	48 weeks	93.0% vs. 93.0%
ATLAS-2M	CAB+RPV QM	CAB+RPV Q2M	Suppressed	522 vs. 523	96 weeks	93.0% vs. 94.0%

2DR: two-drug regimen; LPV/r: ritonavir-boosted lopinavir; 3TC: lamivudine; NRTIs: nucleoside reverse transcriptase inhibitors; ATV/r: ritonavir-boosted atazanavir; DRV/r; ritonavir-boosted darunavir; DTG: dolutegravir; bDRV: boosted darunavir; 3DR: three-drug regimen; FTC: emtricitabine; TDF: tenofovir-disoproxil-fumarate; TAF: tenofovir alafenamide; CAB: cabotegravir; ABC: abacavir; QM: every month; Q2M: every two months.

2.1.1. Protease Inhibitor-Based Regimens

Initial attempts starting around 2000 combined boosted protease inhibitors(PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) but still showed higher levels of toxicity and/or lower efficacy

than triple-drug regimens and led to studies simplifying to a regimen containing a boosted PI and an NRTI [3]. Such switch studies included the open-label GARDEL study, which enrolled 416 patients naive to therapy comparing boosted lopinavir (LPV/r) and lamivudine (3TC) to LPV/r and 2NRTIs [4], and the ATLAS-M study [5], comparing boosted atazanavir (ATV/r) and 3TC in 266 virologically suppressed patients to ATV/r and 2NRTIs; both studies showed non-inferiority by intent to treat analysis. The open-label DUAL study evaluated switching to darunavir boosted with ritonavir (DRV/r) with lamivudine (3TC) in 249 patients virologically suppressed versus continuing a regimen of DRV/r and 2NRTIs. This study demonstrated non-inferiority at 48 weeks between the 2D and 3D regimens (88.9% vs. 92.7%) [6]. Despite these earlier studies, many concerns remained about the durability of the regimens, the inability to utilize them in certain populations such as pregnant women or those with tuberculosis, the concern about adequate suppression of viral reservoirs, the paucity of studies in naïve patients, and some conflicting data that did not show non-inferiority [3].

2.1.2. Integrase Strand Transfer Inhibitor-Based 2DR

With the arrival of the well-tolerated and highly efficacious integrase inhibitor (INSTI) class, several dual-drug regimens incorporating the INSTI class have now demonstrated efficacy, sustained benefit, and tolerability that is non-inferior to triple-drug regimens [7]. Both boosted PI and INSTI regimens and INSTI and NNRTI regimens have been studied with success. The DUALIS study evaluated 263 patients randomly assigned to switch to DRV/r and dolutegravir (DTG) or to continue a darunavir-based three-drug regimen. At 48 weeks, 86.3% vs. 87.9%, respectively, of patients were virologically suppressed [8]. The SWORD 1 and 2 trials which combined evaluated 1028 suppressed patients on various three-drug regimens found that patients randomly assigned to switch to DTG and ripilvirine (RPV) or continue their three-drug regimen had similar outcomes: 95% vs. 95% were suppressed at 48 weeks [9]. This combination was further co-formulated as the drug Juluca®, which is available as a single tablet regimen for the treatment of patients with HIV who are virologically suppressed without a history of resistance to dolutegravir or rilpivirine [10].

2.1.3. Dolutegravir and Lamivudine 2DR

To explore further treatment options that provide long-term safety, tolerability, and ease of use, the combination of DTG and 3TC was studied, initially in small exploratory trials, and later in large double-blind, randomized trials in both virologically suppressed and HIV treatment-naïve patients, and data out to 144 weeks have been recently presented showing sustained non-inferiority. The combined GEMINI 1 and 2 trials enrolled patients who were HIV naïve to therapy and randomly assigned 719 patients to DTG and 3TC vs. 722 patients to DTG and emtricitabine/tenofovir-disoproxil-fumarate (FTC/TDF). At 48 weeks, 91% in the dual therapy arm vs. 93% in the triple-therapy arm achieved, by intent-to-treat analysis, the primary endpoint of virologic suppression to <50 copies/ml [11]. Week 144 results showed that the dual arm continued to meet non-inferiority, with 82% suppressed vs. 84% in the triple-therapy arm [12]. Switch trials have been conducted using DTG/3TC as well. TANGO enrolled virologically suppressed patients who were randomly assigned to switch to DTG/3TC (369 patients) vs. continuing their tenofovir alafenamide (TAF)-based three-drug regimen (372 patients). At the 44th week primary endpoint time of analysis, 93.2% of patients in the dual arm vs. 93% patients in the triple arm achieved a viral load of <50 copies/ml [13]. Again, non-inferiority was maintained through week 144 (86% in the dual arm vs. 84% in the TAF containing triple arm [14]. Another trial, SALSA, enrolled treatment experienced and virologically suppressed patients on various three- and four-drug regimens who were then randomized to switching to DTG/3TC (n = 246) vs. continuing their regimen (n = 247), and at 48 weeks, non-inferiority was met, 94% in the two-drug arm vs. 93% in the three- or four-drug arm [15]. These studies supported a favorable side effect and tolerability profile for DTG/3TC. These drugs are co-formulated as the single-tablet regimen (STR) Dovato®. The use of DTG/3TC or DTG/RPV for simplification in virologically suppressed patients is recommended by the

DHHS, EACS, and GeSIDA guidelines [16–18]. These guidelines also contain recommendations for dual-drug therapies as alternatives in various situations. DTG/3TC is also recommended by these guideline committees as an option for treatment-naïve patients who are Hepatitis B surface antigen negative, have a baseline viral HIV viral load of <500,000 copies/ml, and a CD4 count of >200 cells/mm^3. Addressing the feasibility of starting a regimen of DTG/3TC in patients with a new diagnosis of HIV infection whose baseline laboratories are pending, data on the STAT study was recently published [19]. This is a single-arm, open-label study of DTG/3TC for patients newly diagnosed with HIV who are initiated on ART prior to receiving laboratory confirmation of hepatitis B status, viral load, or HIV-1 genotype. The primary analysis of HIV-RNA <50 copies/ml at week 24 showed 78% of all patients and 92% of patients with available data reached this target.

2.1.4. Long-Acting Intramuscular 2DR

One additional category of dual-drug therapy has entered the market in the novel form of long-acting injectable therapy. Long-acting cabotegravir (CAB-LA), which is an INSTI with a similar structure to DTG, has been studied in combination with a novel formulation of rilpivirine, long-acting rilpivirine (RPV-LA) as injections given intramuscularly on a monthly or every-other-month basis. LATTE-2 was the initial randomized, open-label phase 2b clinical trial that compared CAB + RPV LA as a two-drug HIV-1 maintenance therapy, administered every 4 or 8 weeks to virologically suppressed patients. The injectable regimen was similar to a daily three-drug oral therapy of CAB/abacavir(ABC)/3TC in maintaining viral suppression <HIV-1 RNA <50 copies per/ml through 96 weeks [20]. Together, these results supported phase 3 investigations of CAB + RPV LA in both the FLAIR and ATLAS trials. In FLAIR, patients naïve to antiretroviral therapy (ART) received an induction phase of DTG/ABC/3TC for 20 weeks, and then were randomized to either continue DTG/ABC/3TC or switch to first an oral phase of CBG/RPV and then intramuscular (IM) CAB+RPV-LA monthly [21]. ATLAS enrolled treatment experienced patients who were on 2NTRIs and a 3rd drug and virologically suppressed; patients were then randomly assigned to either continue this oral regimen or switch to an initial oral phase of CAB/RPV as a safety measure and then start CAB-RPV-LA IM monthly [22]. FLAIR and ATLAS combined results showed non-inferiority between the two-drug IM and the three-drug oral arms in ITT analysis at 48 weeks: 93% of 591 patients on the two-drug regimen and 94% of patients on the three-drug regimen had viral loads <50 copies/mL. ATLAS-2M has further extended the analysis of these patients to compare monthly vs. every-other-month injections [23]. At 96 weeks, the monthly and every-other-month injections were non-inferior. Side effects for the injectable regimens have demonstrated a high rate of injection site reactions (ISR), but the majority of these reactions are grade 1 or 2, and treatment discontinuations due to ISRs make up less than 3% across all of these studies. Patient satisfaction surveys have shown that the patients enrolled in these trials overwhelmingly preferred the injectable regimen compared to their former oral regimen, but selection bias may be a factor. Resistance-associated mutations developed in 10 of 522 (1.9%) patients on the every-other-month regimen in ATLAS-2M as opposed to 2 of 523 (<1%) patients on the monthly regimen. Further studies will help to clarify the potential risk for the development of treatment related resistance for monthly vs. every-other-month CAB+RPV-LA regimens.

2.2. Potential Benefits and Risks of 2D Regimens

When considering the potential benefits of fewer drugs in a treatment regimen, the endpoints to consider would be fewer adverse events (AEs) or lower discontinuation rates, favorable renal or metabolic profiles, or differences in weight gain. Two possible other benefits that are difficult to measure are the reduction in future possible drug–drug interactions or the avoidance of as-yet-unrecognized side effects from a drug that is now removed from a regimen. Potential drawbacks must be considered as well. The durability of suppression is one concern, and the data reviewed above support the non-inferiority of the virologic response for certain two-drug regimens

compared to three-drug regimens as far out as 144 weeks. Additional concerns include the possibility of treatment-emergent resistance mutations, low-level viremia, or variability in controlling inflammation and immune activation [3].

2.2.1. Adverse Events and Discontinuation Rates for 2D vs. 3D Regimens

Overall, the 2D regimens discussed above have shown the same rates of the comparison 3D arm in reported AEs, serious AEs, and rates of discontinuation [3]. With regard to more specific endpoints such as changes in metabolic parameters, measurements of renal function, or changes from baseline in weight, the findings are mixed and depend on the particular regimens assessed. However, differences have been small overall and the clinical significance is currently unclear.

2.2.2. Emergence of Resistance Associated Mutations

To protect against the development of treatment-emergent resistance in dual-drug regimens, initial trials were designed as switch trials and recruited patients on suppressive antiretroviral therapy with no history of resistance to the drugs in the regimen. Among several trials evaluating protease inhibitors in dual-drug regimens, the development of resistance mutations to either drug in the regimen was rare, in particular to the protease inhibitor [3]. Regarding the combination of DTG/3TC, in the GEMINI 1 and 2, TANGO, and SALSA trials combined, only one patient developed treatment-emergent virologic resistance [12,13,15]. In these trials, patients with a history of resistance to either drug in the regimen were excluded; however, archive genotypes were not performed on virologically suppressed patients. Two open-label studies are investigating DTG/3TC as a simplification regimen for patients with prior detection of the M184V mutation: the ART-PRO study and the ongoing SOLAR 3D study. The former was a pilot study that enrolled 21 patients with and 21 without a history of prior M184V mutation who were virologically suppressed and naïve to integrase inhibitors, who were then switched to DTG/3TC. At 48 weeks, the virologic response was the same in both groups [24]. The SOLAR 3D study is an open-label prospective trial evaluating the switch to DTG/3TC from a stable baseline two-, three-, or four-drug regimen in patients with historic M184V/I mutation and virologic failure. At 48 weeks by ITT analysis, there were no differences in viral suppression between the arm with prior M184V/I detection or without [25]. Regarding the development of confirmed virologic failure (CVF) for the long-acting combination of CAB-LA and RPV-LA, the overall rate in combined studies of this two-drug therapy as recently presented was about 1% [26]. In individuals with CVF on the every-other-month regimen, 9 of 10 failed with NNRTI RAMs, and 6 of 10 failed with INSTI RAMs, while on the monthly regimen, 2 of 2 patients with CVF had NNRTI and INSTI RAMs at time of failure. A multivariable analysis across Atlas, Flair, and Atlas -2M phase 3 studies revealed that the presence of two or more of four factor was associated with the development of CVF. These four factors were: RPV-resistance-associated mutation(s) at baseline, baseline HIV-1 subtype A6/A1, week 8 RPV trough concentration, and BMI at baseline [26].

2.2.3. Low-Level Viremia and Immune Activation

The analysis for low-level viremia and the presence of inflammation and inflammatory biomarkers have been areas of intense research recently, and multiple studies have been published to try and assess the impact of low-level viremia as well as immune activation [3,27]. However, there is a lack of consensus regarding what constitutes low-level viremia and which biomarkers are validated as indicative of immune activation [27]. Data recently presented from GEMINI 1 and 2 showed no differences in low-level viremia in patients on DTG/3TC compared to a three-drug regimen [28]. It is clear that additional as well as long-term data are needed to better answer these concerns. Unanswered questions due to insufficient or lacking data still remain regarding certain patient populations such as HIV-infected pregnant patients, people co-infected with hepatitis B, or the

performance of these regimens in patients with severe immune depletion or very high viral loads. For these populations, the option of two-drug therapy cannot be recommended without additional clinical trials.

3. Conclusions

Current treatment of HIV is undergoing a paradigm shift as dual-drug therapies are available and recommended for both the initial treatment of naïve populations and for the simplification of therapy in appropriately selected treated populations. The advent of single-tablet regimens and injectable regimens with fewer drugs that maintain efficacy and have favorable tolerability and safety profiles represent viable options for patients and offer additional potential benefits such as fewer drug interactions and lower costs or address the issues of pill fatigue and stigma related to daily ART tablets. Evolving data on the potential concerns around treatment emergent resistance, biomarkers of inflammation, and low-level viremia support the continued exploration of two-drug regimens. Although not all populations at this time can utilize dual-drug regimens, these regimens are now firmly established in the treatment armamentarium of HIV therapeutics.

Funding: This research received no external funding.

Acknowledgments: Many thanks to Harry Poulos, MD who provided administrative support in the preparation of this document.

Conflicts of Interest: The author has received conference or speaker fees from Gilead Sciences, ViiV Healthcare, and Theratechnologies.

References

1. Broder, S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antiviral. Res.* **2010**, *85*, 1–18. [CrossRef] [PubMed]
2. Pau, A.K.; George, J.M. Antiretroviral therapy: current drugs. *Inf. Dis. Clin. N. Am.* **2014**, *28*, 371–402. [CrossRef] [PubMed]
3. Perez-Gonzalez, A.; Suarez-Garcia, I.; Ocampo, A.; Poveda, E. Two-Drug Regimens for HIV—Current Evidence, Research Gaps and Future Challenges. *Microorganisms* **2022**, *10*, 433. [CrossRef] [PubMed]
4. Cahn, P.; Andrade-Villanueva, J.; Arribas, J.R.; Getell, J.M.; Lama, J.R.; Norton, M.; Patterson, P.; Madero, J.S.; Sued, O.; Figueroa, M.I.; et al. Dual Therapy with Lopinavir and Ritonavir plus Lamivudine versus Triple Therapy with Lopinavir and Ritonavir plus Two Nucleoside Reverse Transcriptase Inhibitors in Antiretroviral-Therapy-Naïve Adults with HIV-1 Infection; 48 Week Results of the Randomised, Open Label, non-inferiority GARDEL trial. *Lancet Infect. Dis.* **2014**, *14*, 572–580. [PubMed]
5. di Giambenedetto, S.; Fabbiani, M.; Quiros Roldan, E.; Latini, A.; DEttorre, G.; Antinori, A.; Castagna, A.; Orofino, G.; Francisci, D.; Chinello, P.; et al. Treatment Simplification to Atazanivir/Ritonavir+Lamuvidine versus Maintenance of Atazanivir/Ritonavir plus two NRTIs in Virologically Suppressed HIV-1-Infected Patients: 48 Week Results from a Randomized Trial (ATLAS-M). *J. Antimicrob. Chemother.* **2017**, *72*, 1163–1171. [PubMed]
6. Pulido, F.; Ribera, E.; Lagarde, M.; Perez-Valero, I.; Palacios, R.; Iribarren, J.A.; Payeras, A.; Domingo, P.; Sanz, J.; Cervero, M.; et al. Dual Therapy with Darunavir and Ritonavir Plus Lamivudine vs. Triple Therapy with Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 viral Suppression. *Clin. Infect. Dis.* **2017**, *65*, 2112–2118. [PubMed]
7. Badowski, M.; Perez, S.E.; Silva, D.; Lee, A. Twos a Company, Threes a Crowd: A Review of Initiating or Switching to a Two-Drug Antiretroviral Regimen in Treatment-Naïve and

Treatment-Experienced Patients Living with HIV-1. *Infect. Dis. Ther.* **2020**, *9*, 185–208. [CrossRef] [PubMed]
8. Molina, J.M.; Yazdanpanah, Y.; Afani Saud, A.; Bettacchi, C.; Chahin Anania, C.; DeJesus, E.; Olsen Klopfer, S.; Grandhi, A.; Eves, K.; Robertson, M.N.; et al. Efficacy and Safety of Switching to Dolutegravir with Boosted Darunavir in Virologically Suppressed Adults with HIV-1; A Randomized, Open-Label, Multicenter, Phase 3, Noninferiority Trial: The DUALIS Study. *J. Microbiol. Immunol. Infect.* **2019**, *52*, 1–8.
9. Llibre, J.M.; Hung, C.C.; Brinson, C.; Castelli, F.; Girard, P.M.; Kahl, L.P.; Blair, E.A.; Angelis, K.; Wynne, B.; Vandermeulen, K.; et al. Efficacy, Safety, and Tolerability of Dolutegravir-Rilpivirine for the Maintenance of Virological Suppression in Adults with HIV-1: Phase 3, Randomised, Non-Inferiority SWORD-1 and SWORD-2 Studies. *Lancet* **2018**, *391*, 839–849. [CrossRef]
10. *Juluca [package insert]*; Viiv Healthcare: Raleigh, NC, USA, 2019.
11. Cahn, P.; Madero, J.S.; Arribas, J.R.; Antinori, A.; Ortiz, R.; Clarke, A.E.; Hung, C.-C.; Rockstroh, J.K.; Girard, P.M.; Sievers, J.; et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomized, non-inferiority, phase 3 trials. *Lancet* **2019**, *393*, 143–55. [PubMed]
12. Cahn, P.; Madero, J.S.; Arribas, J.R.; Antinori, A.; Ortiz, R.; Clarke, A.E.; Hung, C.-C.; Rockstroh, J.K.; Girard, P.M.; Sievers, J.; et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection—3 year results from the GEMINI studies. Presented at HIV Drug Therapy, Glasgow, 5–8 October 2020. virtual.
13. van Wyk, J.; Ajana, F.; Bisshop, F.; de Wit, S.; Osiyemi, O.; Portilla Sogorb, J.; Routy, J.P.; Wyen, C.; Ait-Khaled, M.; Nascimento, M.C.; et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose 2-Drug Regimen vs. Continuing a Tenofovir Alafenamide-Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults living with Human Immunodeficiency Virus Type 1: Phase 3, Randomised, Noninferiority TANGO study. *Clin. Infect. Dis.* **2020**, *71*, 1920–1929.
14. Osiyemi, O.; Ajana, F.; Bisshop, F.; De Wit, S.; Portilla, J.; Routy, J.-P.; Wyen, C.; Ait-Khaled, M.; Pappa, K.; Wang, R.; et al. 900. Switching to DTG/3TC Fixed-Dose Combination (FDC) Is Non-inferior to Continuing a TAF-Based Regimen (TBR) in Maintaining Virologic Suppression Through 144 Weeks (TANGO Study). *Open Forum Infect. Dis.* **2021**, *8*, S541. [CrossRef]
15. Llibre, J.M.; Briter, C.A.; Cheng, C.Y.; Osiyemi, O.; Galera, C.; Hocqueloux, L. Switching to the 2-Drug Regimen of Dolutegravir/Lamivudine (DTG/3TC) Fixed-Dose Combination is non-inferior to Continuing a 3-Drug Regimen through 48 weeks in a Randomized Clinical Trial (SALSA). In Proceedings of the 11th IAS Conference on HIV Science, Virtual. 18–21 July 2021. Abstract OALB0303.
16. U.S. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Available online: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf (accessed on 30 May 2022).
17. European AIDS Clinical Society. EACS guidelines version 10.0 (Nov 2019). Available online: http://eacs.sanfordguide.com/ (accessed on 30 May 2022).
18. Executive summary of the GeSIDA/National AIDS Plan consensus document on antiretroviral therapy in adults infected by the human immunodeficiency virus (updated January 2018). *Enfem. Infecc. Microbiol. Clin. (Engl Ed.)* **2019**, *37*, 195–202. [CrossRef]
19. Rolle, C.P.; Berke, M.; Singh, T.; Ortiz, R.; Wurapa, A.; Ramgopal, M.; Leone, P.A.; Matthews, J.E.; Dalessandro, M.; Underwood, M.R.; et al. Dolutegravir/lamuvidine as a first-line regimen in a test-and-treat setting for newly diagnosed people living with HIV. *AIDS* **2021**, *35*, 1957–965. [CrossRef] [PubMed]
20. Margolis, D.A.; Goinzalez-Garcia, J.; Stellbrink, H.J.; Eron, J.J.; Yazdanpanah, Y.; Podzamczer, D.; Lutz, T.; Angel, J.B.; Richmond, G.J.; Clotet, B.; et al. Long-Acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 (LATTE-2): 96-Week Results of a Randomised, Open-Label, Phase 2b, Non-Inferiority Trial. *Lancet* **2017**, *390*, 1499–1510. [CrossRef]
21. Orkin, C.; Bernal Morell, E.; Tan, D.H.S.; Katner, H.; Stelibrink, H.J.; Belonosova, E.; DeMoor, R.; Griffith, S.; Thiagarajah, S.; van Solingen-Ristea, R.; et al. Initiation of Long-Acting Cabotegravir plus Rilpivirine as Direct-to-Injection or with an Oral Lead-in in Adults with HIV-1 Infection: Week 124 Results of the Open-Label Phase 3 FLAIR Study. *Lancet HIV* **2021**, *8*, e668–e678. [CrossRef]
22. Swindells, S.; Andrade-Villanueva, J.F.; Richmond, G.J.; Rizzardini, G.; Baumgarten, A.; Masiá, M.; Latiff, G.; Pokrovsky, V.; Bredeek, F.; Smith, G.; et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N. Engl. J. Med.* **2020**, *382*, 1112–1123. [CrossRef]

23. Overton, E.T.; Richmond, G.; Rizzardini, G.; Jaeger, H.; Orrell, C.; Nagimova, F.; Bredeck, F.; Garcia Deltoro, M.J.; Swindells, S.; Andrade-Villanueva, J.F.; et al. Long-Acting Cabotegravir and Rilpivirine Dosed Every 2 months in Adults with HIV-1 infection (ATLAS-2M), 48 Week Results: A Randomised, Multicentre, Open-Label, Phase 3b, Non-inferiority Study. *Lancet* **2020**, *396*, 1994–2005. [CrossRef]
24. de Miguel, R.; Rial-Crestelo, D.; Dominguez-Dominguez, L.; Montejano, R.; Esteban-Cantos, A.; Aranguren-Rivas, P.; Stella-Ascariz, N.; Bisbal, O.; Bermejo-Plaza, L.; Garcia-Alvarez, M.; et al. Dolutegravir plus Lamivudine for Maintenance of HIV Viral Suppression in Adults with and without Historical Resistance to Lamivudine: 48-Week Results of a Non-Randomized, Pilot Clinical Trial (ART-PRO). *EBioMedicine* **2020**, *55*, 102779. [CrossRef]
25. Blick, G.; Cerreta, E.; Mancini, G.C.A. SOLAR 3D: A Prospective Study Switching to DTG/3TC from 3- or 4-Drug ART for Maintenance of Viral Suppression with Historic M184V/I Mutation and Prior Virological Failures; 48 Week Primary Endpoint Results. In Proceedings of the 18th European AIDS Conference (EACS), London, UK, 27–30 October 2021.
26. Margolis, D.; Schapiro, J.; Perno, C.; Kuritzkes, D.; Quercia, R.; Patel, P.; Polli, J.W.; Cutrell, A.; Dorey, D.; Wang, Y.; et al. A Combination of Viral and Participant Factors Influence Virologic Outcome to Long-Acting Cabotegravir+Rilpivirine; Multivariable and Baseline Factor Analysis Across ATLAS, FLAIR, and ATLAS-2M Phase 3 Studies. In Proceedings of the HIV Drug Therapy Glasgow, Virtual. 5–8 October 2020.
27. van Welzen, G.J.; Oomen, P.G.A.; Hoepelman, A.I.M. Dual Antiretroviral Therap—All Quiet Beneath the Surface? *Front. Immunol.* **2021**, *12*, 637910. [CrossRef] [PubMed]
28. Underwood, M.; Urbaityte, R.; Wang, R.; Horton, J.; Yuan, L.; Wynne, B.; Koteff, J.; van Wyk, J.; Man, C.; Sievers, J. DTG+3TC in Gemini1&-2: HIV-1 Replication at <50 c/ml and VL BLIPS through 144 Weeks. In Proceedings of the 11th IAS Conference on HIV Science, Virtual. 18–21 July 2021; Available online: https://www.natap.org/2021/IAS/IAS_12.htm (accessed on 30 May 2022).