

**EFFECTS OF TENOFOVIR DISOPROXIL FUMURATE/LAMIVUDINE/
DOLUTEGRAVIR (TLD) ON THE HISTOMORPHOMETRIC AND
REPRODUCTIVE PARAMETERS OF THE OVARY, UTERUS, AND PLACENTA
OF ADULT WISTAR RATS**



BY

OGBE, ONOME CLEMENTINA

PG/BMS1818746

**DEPARTMENT OF ANATOMY,
SCHOOL OF BASIC MEDICAL SCIENCES,
COLLEGE OF MEDICAL SCIENCES,
UNIVERSITY OF BENIN,
BENIN CITY.**

SEPTEMBER, 2025

**EFFECTS OF TENOFOVIR DISOPROXIL FUMURATE/LAMIVUDINE/
DOLUTEGRAVIR (TLD) ON THE HISTOMORPHOMETRIC AND
REPRODUCTIVE PARAMETERS OF THE OVARY, UTERUS, AND PLACENTA
OF ADULT WISTAR RATS**

BY

OGBE, ONOME CLEMENTINA

PG/BMS1818746

**A THESIS WRITTEN IN THE DEPARTMENT OF ANATOMY,
SCHOOL OF BASIC MEDICAL SCIENCES, COLLEGE OF MEDICAL SCIENCES,
AND SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES,
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF
DOCTOR OF PHILOSOPHY (Ph.D.) IN ANATOMY OF THE
UNIVERSITY OF BENIN**

SEPTEMBER, 2025

DECLARATION

I declare that:

This thesis report is based on the study undertaken by me in the Department of Anatomy, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Edo State, Nigeria, under the supervision of Prof. J.E Ataman (Project Supervisor) and Dr. V.C Ezeuko (Project Co- Supervisor).

This work has not been previously submitted for the award of a degree.

All ideas and views are essentially based on the research, and where information has been derived from other sources, I confirm that this has been indicated in the thesis.

.....

Ogbe, Onome Clementina

.....

Date

CERTIFICATION OF THESIS ON PLAGIARISM

We the undersigned attest and declare that the thesis undertaken by Ogbe, Onome Clementina
Title: **Effects of Tenofovir Disoproxil Fumurate/Lamivudine/Dolutegravir (TLD) on the
Histomorphometric and Reproductive Parameters of the Ovary, Uterus, and Placenta of
adult Wistar rats.**

Has successfully passed the anti-plagiarism test and does not violate any copyright
regulations.

.....
Name of Project Supervisor/Sign/Date

.....
Name of Project Co-Supervisor/Sign/Date

.....
Dr. A.B. Enogieru
Name of Head of Department/Sign/Date

AUTHOR'S STATEMENT

I hereby grant the University of Benin, through the University of Benin Library, a non-exclusive, worldwide right to reproduce and distribute my thesis and abstract (hereinafter "the Work"), in whole or in part, through any media, in its present form or any translated version for preservation and accessibility, provided such translation does not alter its content. This grant is royalty-free, and I retain the right to publish the Work in its current or future versions elsewhere.

Warranties

I further affirm that:

1. I am the sole author of the Work and grant the University of Benin the right to make it available four (4) years after the award of my doctorate degree, in compliance with the University of Benin Senate regulations.
2. The Work does not contain confidential information requiring third-party consent for disclosure.
3. I have exercised due diligence to ensure that the Work is original and does not breach any Nigerian law or infringe upon any third party's copyright or other Intellectual Property Rights, to the best of my knowledge.
4. Where the Work includes copyrighted material not owned by me, I have obtained unrestricted permission from the copyright holder to grant this license to the University of Benin Library. Such third-party materials are clearly identified and acknowledged within the Work.
5. In the event of any copyright dispute concerning the Work, I agree to indemnify and hold harmless the University of Benin, its officers, employees, and agents from any liability arising from the material authorized under this agreement.
6. The University of Benin is under no obligation whatsoever to take legal action on my behalf as the Depositor in the event of an intellectual property rights infringement or any other related dispute in the material deposited.

Author's Name	Signature/Date	Email
Supervisor's Name	Signature/Date	Email
Co-Supervisor's Name	Signature/Date	Email

CERTIFICATION

This is to certify that this thesis is the original work of Ogbe, Onome Clementina and has been approved in the Department of Anatomy, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Edo State, Nigeria.

.....
Prof. J.E Ataman
Project Supervisor

.....
Date

.....
Dr. V.C Ezeuko
Project Co-Supervisor

.....
Date

.....
Dr. A.B. Enogieru
Head of Department

.....
Date

.....
External Examiner

.....
Date

DEDICATION

First and foremost, I dedicate this thesis to God Almighty for His guidance, provision, and mercy that have sustained me throughout this transformative journey. Secondly, I dedicate it to my beloved mummy, Mrs. Ogbe Grace, and my late daddy, Elder Ogbe Gabriel Edade, whose unwavering support and passion for my education have been a constant source of strength. God bless you.

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to Prof. J. E. Ataman for being an exceptional supervisor and making this thesis journey a truly rewarding experience. You will always remain a significant part of my success story. Your unwavering support, insightful guidance on experimental techniques and data analysis, which you patiently helped me to understand, as well as your genuine interest in this study, have been instrumental in shaping the outcome of this thesis. Your brilliant ideas, expert advice, and dedication in reviewing multiple drafts of this thesis are deeply appreciated. Your constant encouragement to strive for excellence has motivated me to work harder and see this program through to completion.

I am also sincerely thankful to my co-supervisor, Dr. Vitalis Chukwuma Ezeuko, for his valuable insights, contributions, and for generously sharing his knowledge and experience in experimental research. May God bless you all abundantly.

I would like to extend my sincere appreciation to the Head of Department, Dr. A. B. Enogieru, as well as all academic and non-academic staff of the Department of Anatomy, School of Basic Medical Sciences, College of Medical Sciences. Your collective support played a vital role in the successful completion of this thesis. Thank you, and may God bless you all.

I am particularly grateful to Nweke Samuel Monday and Raymond Joseph Enoghase (ALIVE Practical Study) for their assistance during my bench work in the laboratory. Your guidance and insights greatly enhanced the quality of my research - thank you.

My heartfelt thanks go to Mr. Valentine Igbafe for his prayers and words of encouragement, which constantly motivated me to give my best. Your support has meant so much to me. May God continue to bless you.

Special thanks to Mr. Omogbai Wisdom Ohiwerei for your invaluable advice on data analysis and for your continued encouragement and insight - you made this journey significantly smoother and more fulfilling. To the entire staff of Ohilux Global Laboratory and Training Institute, Ekpoma, Edo State - I deeply appreciate your support and contributions. Thank you, and may God bless you all.

I have also been incredibly fortunate to receive unwavering support from friends, especially Dr. Michael Anozie Amadi, Dr. Onyilo Peace Omewomano, Dr. Edem Gabriel Donatus, Dr. Olugbenga Mary Adeola, Mr. Newtons Osarumwense Osagiede, Dr. Akpamu Uwuifor, Dr. Edebiri Ogbemudia Endurance, Dr. Willy Barinem Vidona, and Mr. Blackie Okosun Hassan. Thank you all for your love, friendship, and concern, which kept me grounded and sane throughout this journey.

To my friends who stood by me during the most stressful times - Mr. Okolosi Patani Innocent Edewor, Mrs. Gbobo Dorcas Daunakige Allagoa, Mrs. Godspower Tarikebi, Mrs. Excel Nneka Herrita, Dr. Yembra Aghogho Tarma, and Engr. (Mrs). Uwen John Uduak - thank you for your encouragement and unwavering support in countless ways. May God bless you and your families.

I also extend my deepest appreciation to my colleagues at my workplace, past and present: Dr. William Abiehode, Mr. Sixtus Ojinnaka, Dr. Golda Ezeh, Mrs. Eyaal Alali, Mrs. Okon Peace, Osuo-Odaremete Epow-Aswei Solomon Serene, Ogolo Rubby Abinye, and Emeka Orlu Adna Eze Esther. Your cooperation, encouragement, and patience throughout this journey have been invaluable. Without your support, I could not have completed this Ph.D. successfully.

I remain eternally indebted to Mrs. Oghenegweke Odoh Jessica, Igara Caleb, Igara Abigail, Oghenevwairhe Orunuaherhe, and Orunuaherhe Rosemary. You welcomed a complete stranger into your homes and hearts in Edo State during a time of urgent need, making me feel like family. Your generosity and kindness will never be forgotten.

To Pst. and Pst. (Mrs.) Hope Kalio, Pst. Peter Abadi, Pst. Joshua Dabibi, Pst. and Dr. (Mrs.) Darlington Emeka, and all members of Greater Evangelism World Crusade Sand Filled Church 1, Glorious Centre U.P.E Sand Filled Church 1 (20 Rooms Area), Borokiri, Port Harcourt, Rivers State - thank you for your unwavering prayers throughout my Ph.D. program.

My deepest gratitude goes to my beloved parents, Mr. and Mrs. Ogbe Gabriel Edade. You have been the foundation of my strength and confidence. Your moral, financial, and emotional support - along with your unwavering belief in me - have shaped me into the woman I am today. Though my father is no longer physically present, I still feel his prayers, support, and guidance. Daddy, your words continue to inspire and anchor me. I pray that you rest in the bosom of our Lord Jesus Christ. Mummy, this is your success too - may you live long in health and happiness to witness many more milestones. Words cannot fully express my love and appreciation for you.

Lastly, I want to express heartfelt thanks to my family: Sis. Ogbe Avoezereye Deborah, Mr. and Mrs. Igara, Mr. and Mrs. Ajiroghene Jacob, Enejeta Enifome Julius, Mr. and Mrs. Okoh, Ogbe Omoviagho Elisha, Ogbe Joshua Akpoghene and Mr. and Mrs. Oghenekparobo Enejeta Godwin. Thank you for never doubting my abilities, even when I did. Your constant love, encouragement, and belief in me gave me the strength to push through. May God bless you all. I love you deeply.

This thesis has truly been a collaborative effort, and I am profoundly grateful to everyone who contributed to its realization. Thank you all from the bottom of my heart.

TABLE OF CONTENTS

Title Page	i
Cover page	ii
Declaration	iii
Certification of Thesis on Plagiarism	iv
Author's Statement	v
Certification	vi
Dedication	vii
Acknowledgments	viii
Table of Contents	xii
List of Tables	xxi
List of Figures	xxii
List of Plates	xxiv
Abbreviation	xxvii
Abstract	xxxii
CHAPTER ONE - INTRODUCTION	
1. 1 Background of the Study	1
1.2 Statement of the Problem	4
1.3 Significance of the Study	6
1.4 Aim and Objectives of the Study	6
Aim	6
Objectives	7
CHAPTER TWO - LITERATURE REVIEW	
2.1. Global Statistics on Antiretroviral Therapy Assess	8
2.2 Classification of Antiretroviral Therapy	9

2.2.1. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	10
2.2.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIS)	10
2.2.3 Protease Inhibitors (PIS)	10
2.2.4 Entry Inhibitors	11
2.2.4.1 Fusion Inhibitors (FI)	11
2.2.4.2 Small-Molecule CCR5 Inhibitors	11
2.2.5 Integrase Strand Transfer Inhibitors (INSTI)	11
2.2.6 Pharmacokinetic Enhancer	11
2.3 Mechanism of Action	12
2.4 Drug of Study	13
2.4.1 Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD)	13
2.4.1.1 Characteristics of Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD)	15
2.4.1.2 Adverse Effects	15
2.4.2. Tenofovir Disoproxil Fumarate (TDF)	15
2.4.2.1 Mechanism of Action	16
2.4.2.2 Pharmacokinetics	16
2.4.2.3 Absorption	16
2.4.2.4 Distribution	17
2.4.2.5 Metabolism	18
2.4.2.6 Excretion	18
2.4.2.7 Drug Interactions	18
2.4.2.8 Adverse Effects	19
2.4.3 Lamivudine (3TC)	19
2.4.3.1 Mechanism of Action	20
2.4.3.2 Pharmacokinetics	20

2.4.3.3 Absorption	20
2.4.3.4 Distribution	21
2.4.3.5 Metabolism	21
2.4.3.6 Excretion	21
2.4.3.7 Drug Interactions	22
2.4.3.8 Adverse Effects	22
2.4.4 Dolutegravir (DTG)	22
2.4.4.1 Mechanism of Action	23
2.4.4.2 Pharmacokinetics	23
2.4.4.3 Absorption	23
2.4.4.4 Distribution	24
2.4.4.5 Metabolism	24
2.4.4.6 Excretion	25
2.4.4.7 Drug Interactions	25
2.4.4.8 History	27
2.5 Animal of Study (Wistar rats)	28
2.5.1 Taxonomic Hierarchy	30
2.6 Reproductive System of Female Wistar rats	31
2.6.1 Estrous Cycle in Female Wistar rats	32
2.6.1.1 Proestrus	33
2.6.1.2 Estrus	33
2.6.1.3 Metestrus	34
2.6.1.4 Diestrus	35
2.6.1.5 Endocrine Control of the Oestrous Cycle	36

2.6.1.6 Mating and Reproductive Behaviour in Wistar rats	37
2.6.1.7 Pregnancy Detection in Wistar rats	38
2.6.1.8 Recognition of Pregnancy in Female Wistar rats	39
2.6.1.9 Fertilization and Early Embryonic Development	40
2.4.1.10 Embryo Implantation in Female Wistar rats	41
2.4.1.11 Gestation, Parturition and Weaning	42
2.7 Organs of Study	43
2.7.1 Gross Anatomy of Rats Ovary	43
2.7.2 Gross Anatomy of Rats Uterus	45
2.7.3 Gross Anatomy of Rats Placenta	46
2.8 Gross Anatomy of the Human Ovary	48
2.8.1 The Ligament	49
2.8.2 Vasculature of Ovary	50
2.8.2.1 Arterial Supply	50
2.8.2.2 Venous Drainage	50
2.8.2.3 Lymphatic Drainage	50
2.8.2.4 Innervation	50
2.8.3 Microscopic Anatomy of the Human Ovary	50
2.8.3.1 Medulla	51
2.8.3.2 Cortex	52
2.9 Gross Anatomy of the Human Uterus	52
2.9.1 Divisions	52
2.9.2 Anatomical Position	53
2.9.3 Microscopic Anatomy of the Human Uterus	54
2.9.3.1 Perimetrium	54

2.9.3.2 Myometrium	54
2.9.3.3 Endometrium	55
2.9.3.4 Arterial Supply to the Endometrium	55
2.9.3.4 The Ligaments	55
2.9.3.5 Relations	56
2.9.4 Vasculature of the Uterus	57
2.9.4.1 Arterial Supply	57
2.9.4.2 Venous Drainage	57
2.9.4.3 Lymphatic Drainage	57
2.9.4.4 Innervation	57
2.10 Anatomy of the Human Placenta	58
2.10.1 Surfaces	58
2.10.2 Structural Components	59
2.10.3 Fetoplacental Circulation	60
2.10.4 Maternal-Placental Circulation	61
2.10.5 Functions of the Placenta	61
2.11 Female Fertiliy Hormones	62
2.11.1 Gonadotropic Hormones	62
2.11.2 Prolactin (PRL)	64
2.11.3 Testosterone (T)	65
2.11.4 Progesterone (P4)	69
2.11.5 Estrogens (E2)	71
2.12 Effect of Oxidantive Stress on Female Reproductive System	73
2.13 Ovarian Function	75
2.14 Changes in Endometrium	76

2.15 Embryo Implantation and Placenta	79
2.16 Review of Relevant Literatures on the Effect of Antiretroviral Drugs of Reproductive Parameters	84
CHAPTER THREE - MATERIALS AND METHODS	
3.1 Reagents/Chemicals	96
3.2 Hormone Assay	97
3.3 Equipment/Material	98
3.4 Computer Software	99
3.5 Drugs	100
3.5.1 Determination of Dosage	100
3.5.2 LD50 of Tenofovir Disoproxil Fumurate/Lamivudine/Dolutegravir (TLD)	100
3.5.2.1 Acute Toxicity Study	101
3.5.2.2 Lorke's Method	101
3.5.2.3 Phase 1	101
3.5.2.4 Phase 2	101
3.6 Animal Handling	102
3.7 Research Design	103
3.8 Effect of Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD) on the Hormonal Profile, Antioxidant Status, and Histology of the Ovary and Uterus in unmated adult Wistar rats at the Pregestational Stage of the Experiment	105
3.8.1 Histological Assessment	106
3.8.1.1 Haematoxylin and Eosin Staining Procedures	106
3.8.1.2 Photomicrography	107
3.8.2 Determination of Antioxidant Status at the Pregestational Stage of the Experimental Rats	108

3.8.2.1 Determination of Malondialdehyde (MDA) Concentration	108
3.8.2.2 Determination of Glutathione Peroxidase (GPx) Activity	109
3.8.2.3 Determination of Reduced Glutathione (GSH) Concentration	109
3.8.2.4 Determination of Superoxide Dismutase (SOD) Activity	110
3.8.2.5 Determination of Catalase (CAT) Activity	111
3.8.3 Study on the Hormonal Profile at the Pregestational Stage of the Experimental Rats	113
3.8.3.1 Follicle Stimulating Hormone (FSH)	114
3.8.3.2 Luteinizing Hormone (LH)	115
3.8.3.3 Progesterone (P4)	116
3.8.3.4 Estradiol (E2)	117
3.8.3.5 Testosterone (T)	118
3.8.3.6 Prolactin (PRL)	119
3.9 Effect of Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD) on Implantation and Resorptions at the Gestational Stage of the Experimental Rats	121
3.10 Effect of Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD) on the Placenta at the Gestational Stage of the Experimental Rats	122
3.11 Effect of Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD) on the Number of Live Pups, Size, Weight, Intrauterine Death, and Congenital Anomalies at the Postnatal Stage of the Experimental Rats	123
3.12 Effect of Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD) on the Weight, Size, Neonatal Death/Growth Restriction, and Congenital Anomalies of Pups at postnatal day 28 of the Experimental Rats	124
3.13 Data Analysis	124

CHAPTER FOUR - RESULTS

4.1 Body Weight of the control and treated groups of the Experimental Rats	130
4.2 Ovarian Weight, Uterine Weight, and Uterine Horn Length in control and treated groups at the Pregestational Stage of the Experimental Rats	130
4.3 Histological Findings in Ovary of unmated adult Wistar rats	130
4.4 Histological Findings in Uterus of unmated adult Wistar rats	131
4.5 Evaluation of Ovarian Antioxidant Status at the Pregestational Stage of the Experimental Rats	134
4.6 Evaluation of Uterine Antioxidant Status at the Pregestational Stage of the Experimental Rats	135
4.7 Effect of Treatment on Hormonal Profile at the Pregestational Stage of the Experimental Rats	136
4.8 Effect of Treatment on Implantation/Resorption at the Gestational Stage of the Experimental Rats	136
4.9 Histological Findings of the Uterus in mated adult Wistar rats	137
4.10 Number of Placenta, Placenta Weight, Placenta Diameter, and Thickness at the Gestational Stage of the Experimental Rats	139
4.11 Histological Findings of the Placenta in adult Wistar rats	139
4.12 Evaluation of Placenta Antioxidant Status at the Gestational Stage of the Experimental Rats	141
4.13 Pregnancy Outcome at the Postnatal Stage of the Experimental Rats	142
4.14 Number of Live Pups, Neonatal Death, and Congenital Anomalies of Pups at the Postnatal Stage of the Experimental Rats	142
4.15 Weight of Pups at the Postnatal Stage of the Experimental Rats	142
4.16 Crown-Rump Length of Pups at the Postnatal Stage of the Experimental Rats	143

CHAPTER FIVE - DISCUSSION AND CONCLUSION

5.1 Discussion	172
5.2 Conclusions	203
5.3 Research Findings	203
5.4 Contributions to Knowledge	204
5.5 Recommendations	204
References	206
Appendices	257
Ethnical Approval Certificate	258

-

LIST OF TABLES

Table 3.5.2.1 Record of mortality in phase 1	101
Table 3.5.2.2: Record of mortality in phase 2	102
Table 4.1: Body Weight of the control and treated groups of the Experimental rats	145
Table 4.2: Ovarian Weight, Uterine Weight, and Uterine Horn Length in control and treated groups at The Pregestational Stage of Experimental rats	145
Table 4.3: Measured Uterine Parameters at the Pregestational Stage of the Experimental rats	146
Table 4.4: Ovarian Antioxidant Status at the Pregestational Stage of the Experimental rats	147
Table 4.5: Uterine Antioxidant Status at the Pregestational Stage of the Experimental rats	148
Table 4.6: Hormonal Profile at the Pregestational Stage of the Experimental rats	149
Table 4.7: Implantation of Pups at the Gestational Stage of the Experimental rats	149
Table 4.8: Measured Uterine Parameters at the Gestational Stage of the Experimental rats	150
Table 4.9: Number of Placenta, Placenta Weight, Placenta Diameter and Thickness at the Gestational Stage of the Experimental	151
Table 4.10: Placenta Antioxidant Status at the Gestational Stage of the Experimental rats	152
Table 4.11: Pregnancy Outcome at the Postnatal Stage of the Experimental rats	153
Table 4.12: Number of Live Pups at the Postnatal Stage of the Experimental rats	153
Table 4.13: Weight of Pups at the Postnatal Stage of the Experimental rats	154
Table 4.14: Crown-Rump Length of Pups at the Postnatal Stage of the Experimental rats	155

LIST OF FIGURES

Figure 1: Targets of Antiretroviral Drugs in the HIV Life Cycle	13
Figure 2.1: Chemical structure of Tenofovir Disoproxil Fumarate	16
Figure 2.2: Chemical structure of Lamivudine	19
Figure 2.3: Chemical structure of Dolutegravir	23
Figure 2.4: Taxonomic Hierarchy Wistar rats	30
Figure 2.5: Female Urinogenital system of rat	31
Figure 2.6: Stage of the Wistar rat oestrous cycle	36
Figure 2.7: Hormonal patterns in blood plasma during the rat oestrous cycle	37
Figure 2.8: The three stages of rat implantation, invasion, adhesion, and apposition	43
Figure 2.9: Photomicrographs of rat ovary showing the different developmental stages of ovarian follicles	45
Figure 2.10: Histological cross section of a rat uterine horn	46
Figure 2.11: Histological subgross anatomy of the rat placenta	48
Figure 2.12: Posterior view of the internal female reproductive organs	49
Figure 2.13: Cut section of ovary showing different developmental stages of ovarian follicles, ovulation and degenerating corpus luteum	51
Figure 2.14 Fetus, umbilical cord and placenta (fetal and maternal surfaces)	59
Figure 2.15 Placenta: (A) Maternal surface; (B) Fetal surface	59
Figure 3.1: (A) Weighing of an adult female Wistar rat prior to drug administration. (B) Oral administration of TLD to an adult female Wistar rat	125
Figure 3.2: (C) Weighing of the ovary of an adult female Wistar rat. (D) Measurement of the uterine horn length	125
Figure 3.3: (E) Weighing of the placenta of an adult female Wistar rat. (F) Measurement of the placenta diameter	126

Figure 3.4: (G) Measurement of the placenta thickness	126
Figure 3.5: (H) Weighing of the pups on PND 1. (I) Measurement of the pups CRL	127
Figure 3.6: (J) Weighing of the pups on PND 7. (K) Measurement of the pups CRL	127
Figure 3.7: (L) Weighing of the pups on PND 14. (M) Measurement of the pups CRL	128
Figure 3.8: (N) Weighing of the pups on PND 21. (O) Measurement of the pups CRL	128
Figure 3.9: (P) Weighing of the pups on PND 28. (Q) Measurement of the pups CRL	129

LIST OF PLATES

Plate 4.1: Photomicrograph of the ovary of unmated adult Wistar rats of the control group at the pregestational stage (H&E ×400)	156
Plate 4.2: Photomicrograph of the ovary of unmated adult Wistar rats of the TLD-treated group at the pregestational stage (H&E ×400)	156
Plate 4.3: Photomicrograph of the ovary of unmated adult Wistar rats of the control group at the pregestational stage (H&E ×400)	157
Plate 4.4: Photomicrograph of the ovary of unmated adult Wistar rats of the TLD-treated group at the pregestational stage (H&E ×400)	157
Plate 4.5: Photomicrograph of the uterus of unmated adult Wistar rats of the control group at the pregestational stage (H&E ×100)	158
Plate 4.6: Photomicrograph of the uterus of unmated adult Wistar rats of the TLD-treated group at the pregestational stage (H&E ×100)	158
Plate 4.7: Photomicrograph of the uterus of unmated adult Wistar rats of the control group at the pregestational stage (H&E ×100)	159
Plate 4.8: Photomicrograph of the uterus of unmated adult Wistar rats of the TLD-treated group at the pregestational stage (H&E ×100)	159
Plate 4.9: Photomicrograph of the uterus of unmated adult Wistar rats of the control group at the pregestational stage (H&E ×100)	160
Plate 4.10: Photomicrograph of the uterus of unmated adult Wistar rats of the TLD-treated group at the pregestational stage (H&E ×100)	160
Plate 4.11: Photomicrograph of the uterus of unmated adult Wistar rats of the control group at the pregestational stage showing (H&E ×100)	161
Plate 4.12: Photomicrograph of the uterus of unmated adult Wistar rats of the TLD-treated group at the pregestational stage (H&E ×100)	161

Plate 4.13: Photomicrograph of the uterus of unmated adult Wistar rats of the control group at the pregestational stage (H&E ×100)	162
Plate 4.14: Photomicrograph of the uterus of unmated adult Wistar rats of the TLD-treated group at the pregestational (H&E ×100)	162
Plate 4.15: Photomicrograph of the uterus of mated adult Wistar rats of the control group at the gestational stage (H&E ×400)	163
Plate 4.16: Photomicrograph of the uterus of mated adult Wistar rats of the TLD-treated group at the gestational stage (H&E ×400)	163
Plate 4.17: Photomicrograph of the uterus of mated adult Wistar rats of the control group at the gestational stage (H&E ×400)	164
Plate 4.18: Photomicrograph of the uterus of mated adult Wistar rats of the TLD-treated group at the gestational stage (H&E ×400)	164
Plate 4.19: Photomicrograph of the uterus of mated adult Wistar rats of the control group at the gestational stage (H&E ×400)	165
Plate 4.20: Photomicrograph of the uterus of mated adult Wistar rats of the TLD-treated group at the gestational stage (H&E ×400)	165
Plate 4.21: Photomicrograph of the placenta of mated adult Wistar rats of the control group at the gestational stage (H&E ×400)	166
Plate 4.22: Photomicrograph of the placenta of mated adult Wistar rats of the TLD-treated group at the gestational stage (H&E ×400)	166
Plate 4.23: Photomicrograph of the junctional zone of the placenta in mated adult Wistar rats from the control group at the gestational stage (H&E ×100)	167
Plate 4.24: Photomicrograph of the junctional zone of the placenta in mated adult Wistar rats from the TLD-treated group at the gestational stage (H&E ×100)	167

Plate 4.25: Photomicrograph of the junctional zone of the placenta in mated adult Wistar rats from the control group at the gestational stage (H&E ×400)	168
Plate 4.26: Photomicrograph of the junctional zone of the placenta in mated adult Wistar rats from the TLD-treated group at the gestational stage (H&E ×400)	168
Plate 4.27: Photomicrograph of the placenta of mated adult Wistar rats of the control group at the gestational stage (H&E ×100)	169
Plate 4.28: Photomicrograph of the placenta of mated adult Wistar rats of the TLD-treated group at the gestational stage (H&E ×100)	169
Plate 4.29: Photomicrograph of the placenta of mated adult Wistar rats of the control group at the gestational stage (H&E ×400)	170
Plate 4.30: Photomicrograph of the placenta of mated adult Wistar rats of the TLD-treated group at the gestational stage (H&E ×400)	170
Plate 4.31: Photomicrograph of the placenta of mated adult Wistar rats of the control group at the gestational stage (H&E ×400)	171
Plate 4.32: Photomicrograph of the placenta of mated adult Wistar rats of the TLD-treated group at the gestational stage (H&E ×400)	171

ABBREVIATION

17β-HSD - 17 β -Hydroxysteroid Dehydrogenase	CL - Corpus Luteum
3TC – Lamivudine	CRL - Crown-Rump Length
3TC-MP or L-MP – Lamivudine Mono Phosphate	CY - Cytotrophoblast
3TC-TP or L-TP - Lamivudine Triphosphate	CYP - Carbamoyl Pyridone
3β-HSD - 3 β - Hydroxy Steroid Dehydrogenase	D - Decidua Basalis
A – Androstenedione	Da – Daltons
ACTH - Adenocorticoid Hormone	Dcl - Degenerating Corpus Luteum
AF - Atretic Follicle	dFBV - Dilated Fetal Blood Vessel
AIDS - Acquired Immunodeficiency Syndrome	DHEA – Dehydroepiandrosterone
AMH - Anti-Müllerian hormone	DHEAS - Dehydroepiandrosterone Sulphate
ANOVA - Analysis of Variance	DHT – Dihydrotestosterone
API - Active Pharmaceutical Ingredient	dL - Deciliter
APR - Antiretroviral Pregnancy Registry	dMBV - Dilated Maternal Blood Vessel
ART - Antiretroviral Therapy	DNA - Deoxyribonucleic Acid
ART - Assisted Reproductive Technology	DPX - Dibutylphthalate Polystyrene Xylene
ARVs – Antiretroviral	DR Congo - Democratic Republic of Congo
ATP - Adenine Triphosphate	DTG – Dolutegravir
ATV – Atazanavir	dT4 – Stavudine
AZT – Zidovudine	DTNB - 5, 5-dithio-bis-2-nitrobenzoic acid
BDH - British Drug House	dV - Dilated Vacoulation
BV - Blood vessel	E – Endometrium
C – Control	E1 – Estrone
C₁₀H₁₄N₂O₈ - Ethylenediaminetetraacetic Acid (EDTA)	E2 – Estrogen
C₂H₃O₂CL - Trichloroacetic Acid	E2 – Estradiol
CA - Corpus Albicans	E3 – Estriol
cART - Combination Antiretroviral Therapy	EC - Endometrial Canal
CAT – Catalase	EACS - European Aids Clinical Society
CD4+ cells - Cluster of Differentiation Antigen 4	ECM - Extracellular Matrix
CDC – Centres for Disease Control and Prevention	EDTA - Ethylenediaminetetraacetic Acid
CHMP - Committee for Medicinal Products for Human Use	EE - Exogenous Estrogen
CI - Confidence Interval	EFV – Efavirenz

EG - Endometrial Glands
EGF - Epidermal Growth Factors
ELISA - Enzyme-Linked Immunosorbent Assay
EMA - European Medicine Agency
ENTs - Equilibrate Nucleoside Transporters
Ep - Columnar Epithelium
ERs - Estrogen Receptors
ETR – Etravirine
FA - Follicular Antrum
FB - Fetal Blood
FBV - Fetal Blood Vessel
FC - Follicular Cysts
FDA - United State Food and Drug Administration
FDC - Fixed Dose Combination
FMOH - Federal Ministry of Health
FSH - Follicle Stimulating Hormone
g – Gram
GCI - Glycogen Cell Island
GD - Gestation Day
GF - Graffian Follicle
GnRH - Gonadotropin-Releasing Hormone
GPx - Glutathione Peroxidase
GSH - Reduced Glutathione
H&E - Haematoxylin and Eosin
H₂O₂ - Hydrogen Peroxide
H₂SO₄ - Tetraoxosulphate Acid (VI)
HAART - Highly Active Antiretroviral Therapy
HB-EGF - Heparin Binding-Epidermal Growth Factors
hCG - Human Chorionic Gonadotropin
HCl - Hydrochloric Acid
HIV - Human Immunodeficiency Virus
HLD - Height of Luminal Diameter
hOAT1 - Human Organic Anion Transporters
HPG - Hypothalamus-Pituitary-Gonadal Axis
HUD - Height of Luminal Diameter
ICM - Inner Cell Mass
IFN – Interferon
INSTI - Integrase Strand-Transfer Inhibitors
IUGR - Intrauterine Growth Restriction
IVC - Inferior Venacava
IVF - In-vitro Fertilization
KMnO₄ - Potassium Permanganate
KOH - Potassium Hydroxide
LD₅₀ - Lethal Dose
LH - Luteinizing Hormone
LIF - Leukamea Inhibitory Factors
LMIC - Low and Middle Income Countries
LPV/r - Lopinavir/Ritonavir
LSD - Least Significant Difference
Ltd – Limited
M – Myometrium
MC4R genes - Melanocortin 4 Receptor Genes
MDA – Malondialdehyde
MDR - Multidrug Resistance
MDR4 - Multiple Drugs Resistant
ml – Millilitre
mm – Millimetre
MMP-9 - Matrix Metalloproteinase-9
MS - Maternal Sinusoids
MTCT - Mother-to-Child Transmission
mtDNA - Mitochondrial DNA
MUC-1 - Mucin Like Integral Membrane Protein
Na₂CO₃ - Sodium Carbonate
Na₂HPO₄ - Disodium Phosphate

Na₃C₆H₅O₇ - Sodium Citrate
NACA - National Agency for the Controls of AIDs
NaCl - Sodium Chloride
NaH₂PO₄ - Sodium Dihydrogen Phosphate
NaHCO₃ - Sodium Hydrogen Carbonate
NaH PO₄ - Sodium Hydrogen Phosphate
NaOH - Sodium Hydroxide
NASCP - National AIDS and STIs Control Programme
NFV – Nelfinavir

NIH - National Institutes of Health
nm - Nanometer
NNRTIs - Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs - Nucleoside Reverse Transcriptase Inhibitors
NTD - Neural Tube Defects
O² - Superoxide Anions
OCT2 - Organic Cation Transporter 2
oLC - Occluded Uterine Luminal Canal
OS - Oxidative stress
OS - Ovarian Stroma
OSE - Ovarian Surface Epithelium

P – Perimetrium
P4 – Progesterone
P450 - Cytochrome P450 Protein
PCNA - Proliferating Cell Nuclear Antigen
PCOS - Polycystic Ovary Syndrome
PCP - Pneumocystis Pneumonia
PEP - Post Exposure Prophylaxis
pH - Phosphate Buffer
PI - Protease Inhibitor
PL - Placenta Labyrinth
PL - Human Placenta Lactogen

PLHIV - People Living with HIV
PMS - Premenstrual Syndrome
PMTCT-Prevent the Mother-to-Child Transmission of HIV
PND - Postnatal Day
PR-A - Progesterone Receptor A
PR-B - Progesterone Receptor B
PRL – Prolactin
PW - Placental Weight

RAAS - Renal Renin Angiotensin Aldosterone System
Redox Status - GSH/GSSG
RNA - Ribonucleic Acid
RNS - Reactive Nitrogen Species
ROS - Reactive Oxygen Species
SBP - Systolic Blood Pressure
SEM - Standard Error of Mean
SGA - Small for Gestational Age
SHBG - Sex Hormone-Binding Globulin
SIV - Simian Immunodeficiency Virus
SIVcpz - Simian Immunodeficiency Virus in Chimpanzee
SIVsmm -Simian Immunodeficiency Virus in Sooty Mangabey Monkeys
SOD - Superoxide Dismutase
SOF – Sofosbuvir
SPSS - Statistical Package for Social Sciences
SSEs - Satisfying Sexual Episode
ST – Spongiotrophoblast
StAR - Steroidogenic Acute Regulatory Protein
STI - Sexually Transmitted Infection
SY – Syncytiotrophoblast

T – Testosterone
T – Treated
TAF – Alafenamide

TAF/3TC - Tenofovir Alafenamide/Lamivudine
TB – Tuberculosis
TBA - Thiobarbituric Acid
TCA - Trichloroacetic Acid
TDF - Tenofovir Disoproxil Fumarate
TGC - Trophoblastic Giant Cell
TGF- α - α -Transforming Growth Factors
TLD – Tenofovir Disoproxil Fumarate/Lamivudine/
Dolutegravir
TLE - Tenofovir Disoproxil Fumarate/Lamivudine/
Efavirenz
TP - Total Protein
TSH - Thyroid Stimulating Hormone
 μ M – Micromolar
U - Umbilical Cord
UA - Uterine Arteries
UD - Uterine Diameter
UECs - Uterine Epithelial Cells
UK - United Kingdom
UNAIDS – Joint United Nations Programme on
HIV/AIDS
UNFPA - United Nations Population Fund
USA - United States of America
VSGA - Very Small for Gestational Age
WHO - World Health Organization
WLD - Width of Luminal Diameter
WUD - Width of Uterine Diameter
ZLN - Zidovudine Lamivudine, Nevirapine

ABSTRACT

Human Immunodeficiency Virus (HIV) infection remains one of the leading causes of morbidity and mortality worldwide. Since the beginning of the epidemic, approximately ninety-one million four hundred thousand people have been infected with HIV, and about forty-four million one hundred thousand have died from AIDS-related illnesses. Globally, in 2024, forty million eight hundred thousand people were living with HIV, six hundred thirty thousand people died from AIDS-related illnesses, and one million three hundred thousand people were newly infected with HIV. Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir (TLD) is one of the therapeutic regimens used in the management of HIV infection. This study assessed the effects of TLD on the histomorphometric and reproductive parameters of the ovary, uterus, and placenta of adult Wistar rats. A total of fifty adult female Wistar rats, weighing between 140 g and 194 g, were used for the study. The rats were randomly assigned to control and treated groups, consisting of twenty-five rats, and were further subdivided into five subgroups of five rats each. Both groups received growers mash and distilled water; however, the treated group was administered a daily oral dose of a combination drug consisting of Tenofovir Disoproxil Fumarate (5 mg/kg body weight), Lamivudine (5 mg/kg body weight), and Dolutegravir (0.8 mg/kg body weight) via an orogastric tube. After ninety days of TLD administration, animals with regular four-day estrous cycles were weighed and mated. The animals were categorized into pregestational, gestational, and postnatal groups. The pregestational group was used to evaluate the effects of TLD on antioxidant status, hormonal profile, and histomorphometry of the ovary and uterus. The gestational group was used to assess implantation/resorption, and placenta parameters, while the postnatal group was used to evaluate litter size, litter weight, intrauterine and neonatal death, growth retardation, and congenital anomalies. This study reveals that TLD treatment resulted in a significant decrease in body weight ($p < 0.05$) but did not significantly affect ovarian, uterine weights and uterine horn length ($p > 0.05$). Ovarian antioxidant status showed no significant changes; however, the uterus exhibited reduced malondialdehyde (MDA) levels and increased superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activities. The placenta showed significantly reduced glutathione (GSH) levels. Serum testosterone levels were significantly reduced ($p < 0.05$). No significant differences were observed in litter number, implantation sites, or number of placenta ($p > 0.05$). However, litter size and placenta weights were significantly reduced, with evidence of intrauterine growth retardation and low birth weight. Histological findings revealed impaired follicular maturation characterized by atretic follicles, follicular and luteal cysts, narrowing of the endometrial cavity, and thickened endometrium in the treated group. Additionally, dilation, congestion, and vacuolation of the feto-maternal vascular bed were observed. In conclusion, TLD exerted notable adverse effects on reproductive parameters in female Wistar rats, suggesting the need for caution in its use among women of reproductive age.